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Patent application No.: PA 2003 01418

Date of filing: 30 September 2003

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Titlel: A method of modulating cell survival, differentiation and/or synaptic plasticity

IPC: -

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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

11 October 2004

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PATENT- OG VAREMÆRKESTYRELSEN

A method of modulating cell survival, differentiation and/or synaptic plasticity

Field of invention

The present invention relates to a method of modulating cell differentiation and/or survival by providing compounds comprising fragments from the neural cell adhesion (NCAM) molecule capable of modulating the interaction between the Ig1, Ig2 and/or Ig3 modules of NCAM, wherein said modules derived from two individual NCAM molecules. The invention further relates to a method for screening a candidate compound capable of modulating the interaction between the Ig1, Ig2 and/or Ig3 modules of NCAM and provides an assay for the screening such candidate compound, said assay comprising using a crystal of the Ig1-Ig2-Ig3 module of NCAM. Accordingly, the invention provides a crystalline protein comprising the Ig1-Ig2-Ig3 module of NCAM. The invention also discloses candidate compounds capable of modulating the interaction between the Ig1, Ig2 and/or Ig3 modules of NCAM.

Background of invention

The neural cell adhesion molecule, NCAM, mediates cell-cell adhesion via homophilic (NCAM-NCAM) binding. NCAM plays a key role in neural development, neuronal differentiation and synaptic plasticity, including learning and memory consolidation.

Intercellular interactions play a crucial role in a wide range of biological processes, including cell migration, survival and differentiation. These phenomena depend upon protein recognition at the cell surface mediated by cell-cell adhesion molecules (CAMs).

The neural cell adhesion molecule, NCAM, originally described as a synaptic membrane protein (Jørgensen and Bock, 1974), and later shown to mediate cell-cell adhesion was the first mammalian cell adhesion molecule identified. NCAM belongs to the immunoglobulin (Ig) superfamily. Alternative splicing of mRNA and post-translational modifications generate a large number of NCAM isoforms. The three

major NCAM isoforms have identical extracellular parts consisting of five Ig modules and two fibronectin type III modules.

NCAM is known to mediate Ca^{2+}-independent cell-cell and cell-substratum adhesion via homophilic (NCAM binding to NCAM) and heterophilic (NCAM binding to other molecules) interactions (Berezin et al., 2000). The different modules of NCAM have been shown to perform distinct functions. NCAM binds various extracellular matrix components such as heparin/heparan sulfate, chondroitin sulfate proteoglycans, and different types of collagen. The heparin binding sequence is localized to the Ig2 module. NCAM also binds to the neural cell adhesion molecule L1. This interaction is believed to take place between the fourth Ig module of NCAM and an oligomannosidic moiety expressed on L1.

Despite extensive studies, the precise mechanism of the homophilic binding of NCAM remains unclear, and the published results are to some extent contradictory. NCAM homophilic binding was originally reported to depend on an antiparallel interaction between Ig3 modules from two opposing NCAM molecules. Cell aggregation experiments performed on mouse L-cells expressing chicken NCAM with deletions of different Ig modules indicated an involvement of the Ig3 module. Later, employing microspheres coated with individual recombinant Ig modules of chicken NCAM, binding was demonstrated between the Ig1 and Ig5 modules, and between the Ig2 and Ig4 modules, whereas microspheres coated with Ig3 exhibited strong self-aggregation (Ranheim et al., 1996). However, a study by Atkins et al. (2001) on the solution structure of the Ig3 module of chicken NCAM including ultracentrifugation experiments did not support the suggested dimerization of Ig3.

A binding between recombinant modules of rat Ig1 and Ig2 was demonstrated by means of surface plasmon resonance analysis (Kiselyov et al., 1997). The three-dimensional structures of individual modules of rat Ig1 and Ig2, and the chicken Ig1 module, have been determined by nuclear magnetic resonance (NMR) spectroscopy, resulting in the identification of amino acid residues involved in the homophilic binding between the Ig1 and Ig2 modules (Thomsen et al., 1996; Jensen et al., 1999; Atkins et al., 1999). The crystal structure of the Ig1-2 fragment of rat NCAM provided detailed information on the cross-like Ig1-2 dimer, and pointed out the key residues in this interaction, namely F19 and Y65 (Kasper et al., 2000).

Recently, it was demonstrated that a point mutation of F19 (F19S) did not affect cell aggregation mediated by full length NCAM, even though it abolished dimerization of the Ig1-2-3 fragment, which otherwise takes place in solution (Atkins et al., 2001). These results therefore question the suggested Ig3-to-Ig3 (Rao et al., 1992; Ranheim et al., 1996) and Ig1-to-Ig2 (Kiselyov et al., 1997; Kasper et al., 2000) models of NCAM homophilic binding.

As can be seen from the above, NCAM modules have numerous ways of interacting with other NCAM modules and with non-NCAM molecules. The present invention provides a method of moldulating such interactions by providing compounds capable of binding to NCAM modules.

Summary of invention

Accordingly, the present invention concerns compounds which are capable of modulating proliferation, induce differentiation, and promote regeneration, neuronal plasticity and survival of cells expressing NCAM.

In one aspect the present invention concerns a method of modulating cell differentiation and/or survival of the neural cell adhesion molecule (NCAM) presenting cells comprising

a) providing a candidate compound capable of

i) interacting with the Ig1 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) interacting with the Ig2 module of NCAM, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iv) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

v) interacting with the Ig2 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules,

b) providing at least one NCAM presenting cell;

c) contacting the at least one NCAM presenting cell with said candidate compound, and thereby modulating cell differentiation and/or survival of the at least one NCAM presenting cell.

In another aspect the present invention is concerned with a method for screening whether a candidate compound is capable of modulating cell differentiation and/or survival of NCAM presenting cells by

i) providing a candidate compound;

ii) providing a compound comprising the NCAM Ig1-2-3 module, or fragments of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules;

iii) detecting interaction between the candidate compound of (i) and the compound of (ii).

In still another aspect the present invention provide an assay for selecting a candidate compound capable of modulating cell differentiation and/or survival of NCAM presenting cells, said candidate conpound as above described, comprising the steps of

i) incubating in vitro at least one candidate compound and the second compound, wherein said second compound is the Ig1-2-3 module of NCAM in a solution;

ii) preparing a crystal of a complex of the candidate and second compound by co-crystallisation, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of said second compound or a complex of the second with the fist compound to a resolution at most 5. 0, preferably at most 4. 0, more preferably at most 3. 0 Å, even more preferably at most 1. 5Å;;

iii) determining the three-dimensional structure of the crystal of step (ii) followed by

iv) the selection the candidate compound capable of (1) interacting with the Ig1 module and thereby modulating the interaction between the Ig3 and Ig1 module in the crystal of the Ig1-2-3 module of NCAM , and/or (2) interacting

to the Ig3 module and thereby modulating the interaction between the Ig1 and the Ig3 module in the crystal of the Ig1-2-3 module of NCAM, and/or (3) interacting with the Ig2 module and thereby modulating the interaction between the Ig3 and Ig2 module in the crystal of the Ig1-2-3 module of NCAM and/or (4) interacting with the Ig3 module and thereby modulating the interaction between the Ig2 and Ig3 module in the crystal of the Ig1-2-3 module of NCAM , and/or (5) interacting with the Ig2 module and thereby modulating the interaction of the Ig2 and Ig2 module in the crystal of the Ig1-2-3 module of NCAM;

v) contacting in vitro the candidate compound of step (iv) with a cell expressing NCAM followed by

vi) evaluating the cellular response.

It is an objective of the present invention to provide a crystalline protein comprising the Ig1-2-3 module of NCAM and a method of preparing said crystalline protein.

Moreover, in yet another aspect the invention provides a screening method for selecting a compound capable of modulating cell differentiation and/or survival of NCAM presenting cells, comprising the steps of

i) providing a polypeptide comprising the Ig1-2-3 module of NCAM, or parts of said module such as Ig1, Ig2, Ig3, Ig1-2 or Ig2-3 modules;

ii) generating a structural model of the Ig1-2-3 module of NCAM, or parts of said module such as Ig1, Ig2, Ig3, Ig1-2 or Ig2-3 modules by computer modelling techniques;

iii) designing a compound into the structure of said generated model;

iv) testing a compound of step (iii) in an in vitro or in vivo assay.

In a further aspect of the invention the Ig1-2-3 module of NCAM may be used for the manufacture of a kit for screening a candidate compound capable of modulating NCAM-dependent cell differentiation and/or survival.

The invention also discloses a kit for screening a candidate compound capable of modulating NCAM-dependent cell differentiation and/or survival.

Further, the invention discloses a computer generated model of the crystal structure of the Ig1-2-3 module of NCAM for screening a candidate compound capable of modulating NCAM-dependent cell differentiation and/or survival.

Moreover, the invention provides a compound having the amino acid sequence
WFSPNGEKLSPNQ (SEQ ID NO: 1),
YKCVVTAEDGTQSE (SEQ ID NO: 2),
TLVADADGFPEP (SEQ ID NO: 3),
QIRGIKKTD (SEQ ID NO: 4),
DVR (SEQ ID NO: 5),
RGIKKTD (SEQ ID NO: 6),
DVRRGIKKTD (SEQ ID NO: 7),
KEGED (SEQ ID NO: 8),
IRGIKKTD (SEQ ID NO: 9),
KEGEDGIRGIKKTD (SEQ ID NO: 10),
DKNDE (SEQ ID NO: 11),
TVQARNSIVNAT (SEQ ID NO: 12),
SIHLKVFAK (SEQ ID NO: 13),
LSNNYLQIR (SEQ ID NO: 14),
RFIVLSNNYLQI (SEQ ID NO: 15),
KKDVRFIVLSNNYLQI (SEQ ID NO: 16),
QEFKEGEDAVIV (SEQ ID NO: 17),
KEGEDAVIVCD (SEQ ID NO: 18), or
fragments or variants thereof.

In yet a further embodiment the invention relates to the use of one or more of the above compounds for the manufacture a medicament.

Description of Drawings

Table 1. Crystallographic data and refinement statistics

Table 2. The atomic structure coordinates of the Ig1-2-3 module crystal.

Figure 1. Crystal structure of the rat NCAM Ig1-2-3 fragment at 2.0 Å resolution. **(A)** C□ backbone diagram in stereo with every 10th residue labeled.

(B) Ribbon diagram with β-strands shown in blue and labeled according to Ig I set nomenclature. The $\alpha 3_{10}$ turns are shown in red.

Figure 2. Crystal structure of the Ig1-2-3 fragment of NCAM reveals four major module-module interactions and two kinds of Ig1-2-3 arrays. Space-filling models of interacting Ig1-2-3 cis dimers (mediated by Ig1-Ig2 binding) are shown. The Ig1-to-Ig2, Ig1-to-Ig3, Ig2-to-Ig2, and Ig2-to-Ig3 interaction sites are indicated by white ellipses. The heparin binding sites of the Ig2 modules (residues 133-148) are shown in yellow. The arrows indicate the position of N-linked glycosylation at Asn203 (Asn203 is colored pink). The termini are denoted by N and C.
(A,B) The Ig1-2 mediated cis dimers of the Ig1-2-3 fragment are shown in cyan and green and form a "flat" zipper via an Ig2-to-Ig3 mediated trans interaction, reflecting an interaction between NCAM molecules on opposing cells.
(C,D) The Ig1-2-3 fragment cis dimers also form a non-symmetrical "compact" zipper via Ig1-to-Ig3 and Ig2-to-Ig2 trans interactions. Two cis dimers shown in orange and green are held together by two Ig1-to-Ig3 interactions (full ellipses) on one side and one Ig2-to-Ig2 interaction (stippled ellipse) on the opposite side of the zipper. The views in B and D are perpendicular to A and C, respectively.

Figure 3. Close-up view of the interaction interfaces in the NCAM Ig1-2-3 fragment.
(A) The Ig1-to-Ig2 interaction interface. The Ig1 and Ig2 modules are shown in yellow and green and belong to two different Ig1-2-3 fragments that form one Ig1-2-3 cis dimer.
(B) The Ig2-to-Ig3 interaction interface.
(C) The Ig2-to-Ig2 interaction interface.
(D) The Ig1-to-Ig3 interaction interface. In B-D, the ribbon representations of modules from two interacting Ig1-2-3 fragments belonging to different Ig1-2-3 cis dimers are shown in green and cyan. Oxygen atoms are shown in red and nitrogens in blue. The hydrogen bonds are shown as red dashed lines. Water molecules are shown as red spheres.

Figure 4. The effect of the Ig3 module, the P1-B, P3-DE, P3-G, P3-B peptides, and their derivatives, on neurite outgrowth from the NCAM-expressing PC12-E2 cells grown on top of a confluent monolayer of NCAM-transfected fibroblasts.
(A-F) Confocal micrographs of NCAM-expressing pheochromocytoma PC12-E2 cells

grown on top of a confluent monolayer of vector-transfected **A,C,E** or NCAM-140 transfected **B,D,F** L929 fibroblasts. NCAM-NCAM interaction stimulates neurite outgrowth in PC12-E2 cells grown on top of NCAM-expressing **B** versus NCAM-negative **A** fibroblasts. Introduction of the recombinant Ig3 module does not affect PC12-E2 cells grown on vector-transfected fibroblasts **C** but clearly inhibits neurite outgrowth in PC12-E2 cells grown on NCAM-transfected fibroblasts **D** as a result of disruption of NCAM-NCAM interactions. In contrast, Ig3mut2 neither affects PC12-E2 cells grown on vector-transfected fibroblasts **E** nor inhibits NCAM-induced neurite outgrowth **F**. Peptides P1-B, P3-DE, and P3-G have inhibitory effects comparable to the effect of Ig3wt **C,D**, whereas effects of the Ig3mut1, P3-B peptide, and control peptides are similar to the effect of Ig3mut2 **E,F**. Scale bar, 20 □m.

(G) The effect of the Ig3 module, P1-B, P3-DE, P3-G, P3-B peptides, and their derivatives, is shown in percent of control, setting the difference between the average neurite length of PC12-E2 cells grown on NCAM-140-transfected and vector-transfected fibroblasts to 100%. Results are given as mean ± SEM.* $P<0.05$, ** $P<0.01$ (compared to the induction of neurite outgrowth from PC12-E2 cells grown on top of monolayer of NCAM-transfected fibroblasts).

Figure 5. Schematic representations of the "compact", "flat", and "double" zipper adhesion complexes formed by NCAM, as observed in the crystal structure of the NCAM Ig1-2-3 fragment. The individual Ig modules of Ig1-2-3 are shown as cylinders (Ig1 is red, Ig2 is yellow, and Ig3 is green). The Ig4, Ig5, and the two membrane proximal FnIII modules have been modeled as gray cylinders. Ig and FnIII modules are numbered by Arabic and Roman numerals, respectively. In order to accommodate all seven extracellular modules of NCAM a bend has been introduced after Ig4 according to electron microscopy studies (Hall and Rutishauser, 1987; Becker et al., 1989). The size of the Ig1-2-3 fragment and distance between opposing cell membranes are indicated.

(A) The "compact" zippers are stabilized by Ig1-to-Ig3 and Ig2-to-Ig2 interactions between Ig1-2-3 cis dimers originating from two opposing cell membranes.

(B) The "flat" zipper is stabilized by Ig2-to-Ig3 interactions between Ig1-2-3 cis dimers originating from two opposing cell membranes.

(C) The two types of zippers may co-exist as observed in the crystal and will result in formation of a double zipper-like adhesion complex.

Detailed description of the invention

It is an object of the invention to provide a method for selecting suitable compounds to be used for the promotion of cell differentiation of neural cells and neuronal plasticity, and stimulation of survival and regeneration of neuronal cells.

Molecules with the potential to promote neurite outgrowth as well as stimulate survival, regeneration and modulate proliferation of neuronal cells, such as certain endogenous trophic factors, adhesion molecules, are prime targets in the search for compounds that facilitate for example neuronal regeneration and other forms of neuronal plasticity. To evaluate the potential of the present compounds, the ability to interfere with cell adhesion, stimulate neurite outgrowth, proliferation and regeneration and the survival of neuronal cells may be investigated. It is an object of the present invention to provide compounds capable of binding to one or more positions on the NCAM molecule. In particular, positions in the NCAM Ig1, Ig2 and Ig3 modules are favourable for the promotion of neurite outgrowth. Compounds of the invention are therefore considered to be good promoters of regeneration of neuronal connections, and thereby of functional recovery after damages, as well as promoters of neuronal function in other conditions where such an effect is required.

In the present context "differentiation" is related to the processes of maturation of cells, such as for example extension of neurites from neurons which takes place after the last cell division of said neurons has ended. The compounds of the present invention may be capable of stopping cell division and initiate maturation and/or extension of neurites

In the present invention a compound is considered promising when it is capable of doubling the neurite outgrowth of cultured cells when compared to control cells, such as improving neurite outgrowth three-fold, such as four-fold, for example five fold, such as six-fold.

Further, in the present context the wording "stimulate/promoting survival" is used synonymously with the wording "preventing cell death" or "neuro-protection". By stimulating/promoting survival it is possible to prevent diseases or prevent further

degeneration of the nervous system in individuals suffering from a neuro-degenerative disorder.

"Survival" refers to the process, wherein a cell has been traumatised and would under normal circumstances, with a high probability die, if not the compound of the invention was used to prevent said cell from degenerating, and thus promoting or stimulating survival of said traumatised cell.

By the term "modulation" is meant a change, such as either stimulation or inhibition.

By "modulating NCAM signalling" is meant a molecule capable of initiating the production and/or activation or inhibition of a cascade of messenger molecules leading to a physiological response of the cell, such as for example an increase in neurite length.

The invention further provides for a compound capable of "interfering with cell adhesion". This refers to the process wherein cells are attracted to one another and where the present compound is capable of either stimulating or inhibiting said attraction.

The term "ligand" is defined as a compound, which binds and mimics the compound of the present invention. The ligand may also inhibit naturally occurring interactions, such as by binding to parts of NCAM which are not a part of the binding sites, and wherein the interference is merely a steric interference.

The compounds according to the invention also relates to the prevention of neuronal cell death. Peripheral nerve cells possess to a limited extent a potential to regenerate and re-establish functional connections with their targets after various injuries. However, functional recovery is rarely complete and peripheral nerve cell damage remains a considerable problem. In the central nervous system, the potential for regeneration is even more limited. Therefore, the identification of substances with the ability to prevent neuronal cell death in the peripheral and the central nervous system is significant and of great commercial value.

In a further embodiment of the invention the compounds may comprise other chemical entities, such as sugar, cholesterol, and fatty acid. Preferably, the chemical entity is bound to the N-terminal or C-terminal of the peptide of the compound.

It is an aspect of the present invention that the compounds are capable of binding to the NCAM Ig1 and/or Ig2 and/or Ig3 modules at a homophilic binding site, or at any other sites of the module mimicking the effect of the binding at a homophilic binding site, or modulating said effect.

Without being bound by theory, the present inventors believe that active ligands to the NCAM Ig1 and/or Ig2 and/ Ig3 modules are ligands which bind to the NCAM Ig1 and/or Ig2 and/or Ig3 modules and thus trigger a conformational change of the module resulting in a signalling cascade being initiated, wherein said signalling results in a physiological change in the cell, such as influencing proliferation of cells and/or neurite outgrowth. Thus, a compound according to the invention may be any compound described above which can trigger a conformational change of the NCAM Ig1 and/or the NCAM Ig2 and/or the NCAM Ig3 module resulting in a downstream signalling cascade.

Method of modulating

Thus, it is an object of the present invention to provide a method of modulating cell differentiation and/or survival of the neural cell adhesion molecule (NCAM) presenting cells by

a) providing a candidate compound capable of

i) interacting with the Ig1 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) interacting with the Ig2 module of NCAM, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

vi) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

vii) interacting with the Ig2 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules,

b) providing at least one NCAM presenting cell;

c) contacting the at least one NCAM presenting cell with said candidate compound, and thereby modulating cell differentiation and/or survival of the at least one NCAM presenting cell.

In the present context the term "mimicking" means that the compound of the invention is acting as a ligand binding to the Ig1, Ig2 or Ig3 module, respectively, and is thereby replacing the binding to these modules of another the Ig3, Ig2 or Ig1 modules, respectfully, as described above. The present inventors present a model for NCAM homophilic binding, wherein the Ig1 and Ig2 modules mediate dimerization of NCAM molecules situated on the same cell surface (*cis* interaction), and wherein the Ig3 module mediates interactions between NCAM molecules expressed on the surface of opposing cells (*trans* interaction) through simultaneous binding to the Ig1 and Ig2 modules. This arrangement results in the formation of a double zipper-like NCAM adhesion complex.

Sequences from NCAM

In one embodiment the cell differentiation and/or survival are mediated by NCAM.

In another embodiment a candidate compound of the invention may be selected from the group comprising peptide fragments, or variants of the peptide fragments derived from the sequence of NCAM.

According to the invention a preferred candidate compound is selected from the group comprising peptide fragments, or variants of said fragments, selected from the group comprising amino acid sequences

WFSPNGEKLSPNQ (SEQ ID NO: 1)

YKCVVTAEDGTQSE (SEQ ID NO: 2)

TLVADADGFPEP (SEQ ID NO: 3)

QIRGIKKTD (SEQ ID NO: 4)
DVR (SEQ ID NO: 5)
RGIKKTD (SEQ ID NO: 6)
DVRRGIKKTD (SEQ ID NO: 7
KEGED (SEQ ID NO: 8)
IRGIKKTD (SEQ ID NO: 9)
KEGEDGIRGIKKTD (SEQ ID NO: 10)
DKNDE (SEQ ID NO: 11)
TVQARNSIVNAT (SEQ ID NO: 12)
SIHLKVFAK (SEQ ID NO: 13)
LSNNYLQIR (SEQ ID NO: 14)
RFIVLSNNYLQI (SEQ ID NO: 15)
KKDVRFIVLSNNYLQI (SEQ ID NO: 16)
QEFKEGEDAVIV (SEQ ID NO: 17)
KEGEDAVIVCD (SEQ ID NO: 18)
GEISVGESKFFL (SEQ ID NO: 19)
KHIFSDDSSELTIRNVDKNDE (SEQ ID NO: 20),

or combinations thereof, wherein said amino acid sequences are derived from the sequence of rat NCAM having the NCBI accession number NP_113709 (SEQ ID NO: 40).

The NCAM of the invention is mammalian NCAM, or variants, or fragments thereof. In a preferred embodiment the NCAM may be human NCAM having the NCBI accession number P13591, or variants, or fragments thereof.

In the present context the "fragment thereof" is to be understood as being any part of the NCAM molecule or any part of the present compound capable of interacting with the Ig1, Ig2 and/or Ig3 modules of NCAM and through said binding modulate proliferation, and/or induce differentiation, and/or stimulate regeneration, neuronal plasticity and/or survival of cells.

The "variant thereof" is to be understood as being any peptide sequence capable of interacting with the Ig1, Ig2 and/or Ig3 modules of NCAM, and via said binding induce differentiation, modulate proliferation, stimulate regeneration, neuronal plasticity and survival of cells. Thus, fragment or variant may be defined as

i) Fragments/variants comprising an amino acid sequence capable of being recognised by an antibody also capable of recognising the predetermined NCAM amino acid sequence, and/or

ii) Fragments/variants comprising an amino acid sequence capable of binding to a receptor moiety also capable of binding the predetermined NCAM amino acid sequence, and/or

iii) Fragments/variants having at least a substantially similar binding affinity to at least one of the Ig1, Ig2 or Ig3 modules as said predetermined NCAM amino acid sequence.

In the present context the term "functional equivalent" means a variant as defined above.

The binding affinity of the compound according to the invention preferably has a binding affinity (Kd value) to the NCAM modules in the range of 10^{-3} to 10^{-10} M, such as preferably in the range of 10^{-4} to 10^{-8} M. According to the present invention the binding affinity is determined by one of the following assays of surface plasmon resonance analysis or nuclear magnetic resonance spectroscopy.

In one embodiment variants may be understood as exhibiting amino acid sequences gradually differing from the preferred predetermined sequence, as the number and scope of insertions, deletions and substitutions including conservative substitutions increase. This difference is measured as a reduction in homology between the predetermined sequence and the variant.

The peptides may be modified, for example by substitution of one or more of the amino acid residues. Both L-amino acids and D-amino acids may be used. Other modification may comprise derivatives such as esters, sugars, etc. Examples are methyl and acetyl esters. Polymerisation such as repetitive sequences or attachment to various carriers are well-known in the art, e.g. lysine backbones, such as lysine dendrimers carrying 4 peptides, 8 peptides, 16 peptides, or 32 peptides. Other carriers may be protein moieties, such as bovine serum albumin (BSA), or lipophilic dendrimers, or micelle-like carriers formed by lipophilic derivatives, or starburst (star-like) carbon chain polymer conjugates, or ligand presenting assembly (LPA) based on derivatives of diethylaminomethane.

Variants of the fragments according to the invention may comprise, within the same variant, or fragments thereof or among different variants, or fragments thereof, at least one substitution, such as a plurality of substitutions introduced independently of one another. Variants of the complex, or fragments thereof may thus comprise conservative substitutions independently of one another, wherein at least one glycine (Gly) of said variant, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Ala, Val, Leu, and Ile, and independently thereof, variants, or fragments thereof, wherein at least one alanine (Ala) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Gly, Val, Leu, and Ile, and independently thereof, variants, or fragments thereof, wherein at least one valine (Val) of said variant, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Gly, Ala, Leu, and Ile, and independently thereof, variants, or fragments thereof, wherein at least one leucine (Leu) of said variant, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Gly, Ala, Val, and Ile, and independently thereof, variants, or fragments thereof, wherein at least one isoleucine (Ile) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Gly, Ala, Val and Leu, and independently thereof, variants, or fragments thereof wherein at least one aspartic acids (Asp) of said variant, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Glu, Asn, and Gln, and independently thereof, variants, or fragments thereof, wherein at least one aspargine (Asn) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Asp, Glu, and Gln, and independently thereof, variants, or fragments thereof, wherein at least one glutamine (Gln) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Asp, Glu, and Asn, and wherein at least one phenylalanine (Phe) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Tyr, Trp, His, Pro, and preferably selected from the group of amino acids consisting of Tyr and Trp, and independently thereof, variants, or fragments thereof, wherein at least one tyrosine (Tyr) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Phe, Trp, His, Pro, preferably an amino acid selected from the group of amino acids consisting of Phe and Trp,

and independently thereof, variants, or fragments thereof, wherein at least one arginine (Arg) of said fragment is substituted with an amino acid selected from the group of amino acids consisting of Lys and His, and independently thereof, variants, or fragments thereof, wherein at least one lysine (Lys) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Arg and His, and independently thereof, variants, or fragments thereof, and independently thereof, variants, or fragments thereof, and wherein at least one proline (Pro) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Phe, Tyr, Trp, and His, and independently thereof, variants, or fragments thereof, wherein at least one cysteine (Cys) of said variants, or fragments thereof is substituted with an amino acid selected from the group of amino acids consisting of Asp, Glu, Lys, Arg, His, Asn, Gln, Ser, Thr, and Tyr.

Thus, judging from the above outline that the same equivalent or fragment thereof may comprise more than one conservative amino acid substitution from more than one group of conservative amino acids as defined herein above.

Substitutions.

Conservative substitutions may be introduced in any position of a preferred predetermined peptide of the invention or fragment thereof. It may however also be desirable to introduce non-conservative substitutions, particularly, but not limited to, a non-conservative substitution in any one or more positions.

A non-conservative substitution leading to the formation of a functionally equivalent fragment of the peptide of the invention would for example differ substantially in polarity, for example a residue with a non-polar side chain (Ala, Leu, Pro, Trp, Val, Ile, Leu, Phe or Met) substituted for a residue with a polar side chain such as Gly, Ser, Thr, Cys, Tyr, Asn, or Gln or a charged amino acid such as Asp, Glu, Arg, or Lys, or substituting a charged or a polar residue for a non-polar one; and/or ii) differ substantially in its effect on peptide backbone orientation such as substitution of or for Pro or Gly by another residue; and/or iii) differ substantially in electric charge, for example substitution of a negatively charged residue such as Glu or Asp for a positively charged residue such as Lys, His or Arg (and vice versa); and/or iv) differ substantially in steric bulk, for example substitution of a bulky residue such as His,

Trp, Phe or Tyr for one having a minor side chain, e.g. Ala, Gly or Ser (and vice versa).

Substitution of amino acids may in one embodiment be made based upon their hydrophobicity and hydrophilicity values and the relative similarity of the amino acid side-chain substituents, including charge, size, and the like. Exemplary amino acid substitutions which take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

Addition/deletion

The addition or deletion of an amino acid may be an addition or deletion of from 2 to preferably 10 amino acids, such as from 2 to 8 amino acids, for example from 2 to 6 amino acids, such as from 2 to 4 amino acids. However, additions of more than 10 amino acids, such as additions from 2 to 10 amino acids, are also comprised within the present invention. In the multimeric forms additions/deletions may be made individually in each monomer of the multimer.

Non-peptides

The invention also concerns non-peptide variants of the compounds disclosed herein. In particular, such variants should be understood to be compounds which bind to or in other ways interact with the Ig1, Ig2 or the Ig3 modules of NCAM and thereby stimulate Ig1, Ig2 or Ig3 signalling and/or modulate proliferation and/or induce differentiation and/or stimulate regeneration, neuronal plasticity and/or survival of cells presenting an NCAM receptor.

Functional equivalent

It will thus be understood that the invention concerns a compound comprising at least one fragment capable of binding at least one receptor, or a variant thereof including any variants and functional equivalents of such at least one fragment.

A functional equivalent obtained by substitution may well exhibit some form or degree of native NCAM activity, and yet be less homologous, if residues containing functionally similar amino acid side chains are substituted. Functionally similar in the present respect refers to dominant characteristics of the side chains such as

hydrophobic, basic, neutral or acidic, or the presence or absence of steric bulk. Accordingly, in one embodiment of the invention, the degree of identity between i) a given functional equivalent capable of effect and ii) a preferred predetermined fragment, is not a principal measure of the fragment as a variant or functional equivalent of a preferred predetermined peptide fragment according to the present invention.

Fragments sharing at least some homology with a preferred predetermined fragment of at least 3 amino acids, more preferably at least 5 amino acids, are to be considered as falling within the scope of the present invention when they are at least about 25 percent homologous with the preferred predetermined NCAM peptide, or fragment thereof, such as at least about 30 percent homologous, for example at least about 40 percent homologous, such as at least about 50 percent homologous, for example at least about 55 percent homologous, such as at least about 60 percent homologous, for example at least about 65 percent homologous, such as at least about 70 percent homologous, such as at least about 75 percent homologous, for example at least about 80 percent homologous, such as at least about 85 percent homologous.
Sequence identity can be measured using sequence analysis software (for example, the Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Centre, 1710 University Avenue, Madison, WI 53705), with the default parameters as specified therein.

Where nothing is specified it is to be understood that the C-terminal amino acid of a polypeptide of the invention exists as the free carboxylic acid, this may also be specified as "-OH". However, the C-terminal amino acid of a compound of the invention may be the amidated derivative, which is indicated as "-NH_2". Where nothing else is stated the N-terminal amino acid of a polypeptide comprise a free amino-group, this may also be specified as "H-".

Where nothing else is specified amino acid can be selected from any amino acid, whether naturally occurring or not, such as alpha amino acids, beta amino acids, and/or gamma amino acids. Accordingly, the group comprises but are not limited to: Ala, Val, Leu, Ile, Pro, Phe, Trp, Met, Gly, Ser, Thr, Cys, Tyr, Asn, Gln, Asp, Glu, Lys, Arg,His Aib, Nal, Sar, Orn, Lysine analogues DAP and DAPA, 4Hyp

Method for screening

According to the present invention, compounds may be identified by a method for screening whether said compounds are capable of modulating cell differentiation and/or survival of NCAM presenting cells by

i) providing a candidate compound;

ii) providing a compound comprising the NCAM Ig1-2-3 module, or fragments of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules;

iii) detecting interaction between the candidate compound of (i) and the compound of (ii).

In a preferred embodiment of the invention the compound of (ii) is represented by the Ig1-2-3 module of NCAM comprising a consecutive sequence of at least 289 amino acids from the sequence of NCAM. In more preferred embodiment the sequence comprises aa 1 to 289 of NCAM, wherein NCAM is rat NCAM having the NCBI accession number NP_113709 identified as SEQ ID NO: 40 of the present application.

By the "Ig1-2-3 module of NCAM" in the present context is meant a contiguous amino acid sequence as described above consisting of the sequences of Ig1, Ig2, and Ig3, and linker sequences connecting said modules in the following order: N-terminus<Ig1-linker-Ig2-linker-Ig3 >C-terminus.

By the term "candidate compound" in the present context is meant a compound which is identified by the above method and selected by a screening assay or screening methods described below.

According to the present invention, the candidate compound may be any molecule capable of modulating neuronal differentiation and/or survival as described above. Such a compound may, for example, be selected from the group comprising combinatorial libraries of peptides, lipids, carbohydrates or other organic molecules, or co-polymers of amino acids with other organic compounds. In a preferred embodiment, the candidate compound of the invention is a peptide.

The purpose of the above screening method is for identification and selection of interesting compounds (candidate compound) capable of interacting with the Ig1-2-3 module of NCAM, or fragments thereof, (second compound) and thereby modulating NCAM-dependent cell differentiation and/or survival.

Solution

In one embodiment of the invention the second compound is a solution. In a preferred embodiment the solution of the second compound is an aquatic solution. In a more preferred embodiment the solution of the second compound is phosphate buffered saline (PBS) solution or a TRIS-HCl buffer, pH 7.4.

Crystal

Yet in a further embodiment the second compound of the invention comprises a crystalline protein comprising the Ig1-2-3 module of NCAM.

Crystal

A crystal of the Ig1-2-3 module of NCAM having the amino acid sequence corresponding to amino acid residues 1-289 of rat NCAM (NCBI accession number NP_113709; SEQ ID NO: 40) should according to the present invention be preferably used for the purpose of the above screening method. Determining the structure of said crystal should be done using X-ray diffraction.

In a preferred embodiment the crystal is a crystal of a polypeptide comprising the Ig1-2-3 module of NCAM comprising a homophilic binding site of NCAM. The crystal may comprise more than one polypeptide, for example two polypeptides. In a preferred embodiment the crystal comprises the Ig1, Ig2 and Ig3 modules of NCAM co-jointed in one fragment by interconnecting amino acid sequences, said one fragment termed herein "the Ig1-2-3 fragment".

Hence, it is preferred that the crystal diffracts X-rays for determination of atomic co-ordinates to a resolution of at least 4 Å, preferably at least 3 Å, more preferably at least 2.8 Å, even more preferably at least 2.5 Å, most preferably at least 2.0 Å.

In a very preferred embodiment of the invention the crystal comprises atoms arranged in a spatial relationship represented by the structure co-ordinates of table 2, or by co-ordinates having a root mean square deviation there from of not more than 2.5 Å, preferably not more than 2.25 Å, more preferably not more than 2.0 Å, even more preferably not more than 1.75 Å, yet more preferably not more than 1.5 Å, for example not more than 1.25 Å, such as not more than 1.0 Å. Preferably, the co-ordinates has a root mean square deviation there from, of not more than 2.5 Å, preferably not more than 2.25 Å, more preferably not more than 2.0 Å, even more preferably not more than 1.75 Å, yet more preferably not more than 1.5 Å, for example not more than 1.25 Å, such as not more than 1.0 Å.

Preferably, the crystal comprises or more preferably consists of the structure as deposited to the PDB with id 1QZ1.

The crystal may comprise more than one polypeptide of the Ig1-2-3 fragment NCAM per asymmetric unit, in a preferred embodiment of the invention the crystal comprises polypeptides of the one Ig1-2-3 module of NCAM per asymmetric unit.

It is preferred that the crystal has unit cell dimensions of in the range of
a=50 to 52, preferably 50.5 to 51.0, more preferably around 51.5
b=107.5 to 109.5, preferably 108 to 109, more preferably around 108.5
c=146 to 151, preferably 148 to 150, more preferably around 149.0
α=85.5 to 95.5, preferably 88 to 92, more preferably around 90
β=85.5 to 95.5, preferably 88 to 92, more preferably around 90
γ=85.5 to 95.5, preferably 88 to 92, more preferably around 90.

Most preferably the crystal has the following characteristics:

Spacegroup: $I2_12_12_1$ with 1 molecule per asymmetric unit,
unit cell dimensions of a=51.5 b=108.5 c=149.0 Å alpha=90° beta=90° gamma=90°.

Preparing crystals

After several unsuccessful attempts, suitable conditions for preparing crystals of a polypeptide corresponding to the Ig 1-2-3 module of NCAM were identified.

It is therefore also an aspect of the present invention to provide a crystal comprising a polypeptide comprising at least 289 consecutive amino acid residues corresponding to amino acid residues 1-289 of rat NCAM (NCBI accession number NP_113709) (SEQ ID NO: 40), said consecutive amino acids correspond to the Ig1-2-3 fragment of rat NCAM using a method of preparing a crystal, wherein said method comprises the steps of

i) providing said polypeptide;

ii) growing crystals under conditions wherein said polypeptide is incubated in a buffer comprising in the range of 14 to 17% polyethylene glycol 4000 (PEG4k), in the range of 0.150 M to 0.5 M Li sulfate salt wherein said buffer has a pH in the range of 4.8 – 5.8;

iii) thereby preparing said crystals

In one embodiment of the invention, co-crystals of said polypeptide and a compound capable of interacting with said polypeptide are prepared. Said compound may have been identified by any of the methods outlined herein below. Hence, the compound may in one aspect of the invention be a modulator, such as a modulator of NCAM-homophilic interaction mediated by the Ig 1-2-3 module of NCAM.

The co-crystals are useful for designing optimised compounds, with enhanced binding properties. In particular, the co-crystals may be useful for designing better inhibitors of homophilic interaction mediated by the Ig 1-2-3 module of NCAM, or stabilizers of said interaction.

The buffer preferably comprises in the range of 5 to 25% polyethylene glycol, more preferably in the range of 10 to 20%, even more preferably in the range of 12 to 18%, yet more preferably in the range of 14 to 16 %, most preferably around 15% polyethylene glycol. Polyethylene glycol (PEG) may be any suitable PEG for example a PEG selected from the group consisting of PEG 4000, PEG 6000 and PEG 8000, preferably polyethylene glycol is PEG 4000.

The buffer preferably comprises in the range of 0.15 M to 0.5 M salt, more preferably in the range of 0.2 to 0.5 M, even more preferably in the range of 0.3 to 0.5 M, yet more preferably in the range of 0.4 to 0.5 M, most preferably around 0.45 M salt. The salt may be any useful salt, preferably the salt is Li sulfate (Li_2SO_4)

The buffer preferably has a pH in the range of 4.0 to 8.5, more preferably in the range of 4.5 to 7.5, even more preferably in the range of 5.0 to 6.5, yet more preferably in the range of 5.0 to 5.2. The buffer may be any useful buffer, preferably the Na-acetate buffer.

Incubation should be performed at a suitable temperature, preferably at a temperature in the range of 5 to 25°C, more preferably in the range of 10 to 25°C, even more preferably in the range of 15 to 25°C, even more preferably in the range of 17 to 21°C, yet more preferably around 18°C.

The crystals may be grown by any suitable method, for example by the hanging drop method.

Determination of structure

The structure of crystals may be determined by any method known to the person skilled in the art, for example using X-ray diffraction. Once a structure has been identified, said structure may be refined using suitable software.

In one embodiment of the invention a molecular replacement technique may be used. Such techniques involves that the structure is determined by obtaining x-ray diffraction data for crystals of the polypeptide or complex for which one wishes to determine the three dimensional structure. Then, one determines the three-dimensional structure of that polypeptide or complex by analysing the x-ray diffraction data using molecular replacement techniques with reference to known structural co-ordinates of a structurally similar protein. In the case of polypeptide comprising the Ig1-2 modules of NCAM, structural co-ordinates of said modules may be used. As described in U.S. Pat. No. 5,353,236, for instance, molecular replacement uses a molecule having a known structure as a starting point to model the structure of an unknown crystalline sample. This technique is based on the principle that two molecules, which have similar structures, orientations and positions in the unit cell, diffract similarly. Molecular replacement involves positioning the known structure in the unit cell in the same location and orientation as the unknown structure. Once positioned, the atoms of the known structure in the

unit cell are used to calculate the structure factors that would result from a hypothetical diffraction experiment. This involves rotating the known structure in the six dimensions (three angular and three spatial dimensions) until alignment of the known structure with the experimental data is achieved. This approximate structure can be fine-tuned to yield a more accurate and often higher resolution structure using various refinement techniques. For instance, the resultant model for the structure defined by the experimental data may be subjected to rigid body refinement in which the model is subjected to limited additional rotation in the six dimensions yielding positioning shifts of under about 5%. The refined model may then be further refined using other known refinement methods.

Another method for determining the three-dimensional structure of a polypeptide corresponding to the Ig 1-2-3 module of NCAM, or a complex of said polypeptide with an interacting compound, is homology modelling techniques. Homology modelling involves constructing a model of an unknown structure using structural co-ordinates of one or more related proteins, protein domains and/or subdomains. Homology modelling may be conducted by fitting common or homologous portions of the protein or peptide whose three dimensional structure is to be solved to the three dimensional structure of homologous structural elements. Homology modelling can include rebuilding part or all of a three dimensional structure with replacement of amino acids (or other components) by those of the related structure to be solved.

An example of structure determination is outlined in example 2.

Structural coordinates of a crystalline polypeptide of this invention may be stored in a machine-readable form on a machine-readable storage medium, e.g. a computer hard drive, diskette, DAT tape, CD-ROM etc., for display as a three-dimensional shape or for other uses involving computer-assisted manipulation of, or computation based on, the structural coordinates or the three-dimensional structures they define. For example, data defining the three dimensional structure of a polypeptide corresponding to the Ig 1-2-3 module of NCAM, may be stored in a machine-readable storage medium, and may be displayed as a graphical three-dimensional representation of the protein structure, typically using a computer capable of reading the data from said storage medium and programmed with instructions for creating the representation from such data. This invention thus encompasses a machine,

such as a computer, having a memory that contains data representing the structural coordinates of a crystalline composition of this invention, e.g. the coordinates set forth in table 2, together with additional optional data and instructions for manipulating such data. Such data may be used for a variety of purposes, such as the elucidation of other related structures and drug discovery.

A first set of such machine readable data may be combined with a second set of machine-readable data using a machine programmed with instructions for using the first data set and the second data set to determine at least a portion of the coordinates corresponding to the second set of machine-readable data. For instance, the first set of data may comprise a Fourier transform of at least a portion of the coordinates for the complex set forth in table 2, while the second data set may comprise X-ray diffraction data of a molecule or molecular complex.

More specifically, one of the objects of this invention is to provide three-dimensional structural information of co-complexes comprising the homophilic binding site of the Ig 1-2-3 module of NCAM. To that end, we provide for the use of the structural co-ordinates of a crystalline composition of this invention, or portions thereof, to solve, e.g. by molecular replacement or by homology modelling techniques, the three dimensional structure of a crystalline form of another similar cell adhesion molecule (CAM), for example another CAM comprising the Ig modules capable of homophilic interaction or a polypeptide:interacting compound complex.

For example, one may use molecular replacement to exploit a set of coordinates such as set forth in table 2 to determine the structure of a crystalline co-complex of a polypeptide corresponding to the Ig 1-2-3 module of NCAM comprising a homophilic binding site and an interacting compound.

Uses of the structures

A 3D representation of the polypeptides described in the present invention may be useful for several purposes, for example for determining the structure of similar proteins or polypeptides (see also herein above) or for designing compounds capable of interacting with said polypeptides.

For example, the three dimensional structure defined by the machine readable data for the polypeptide of the Ig 1-2-3 module of NCAM may be computationally evaluated for its ability to associate with various chemical entities or test compounds. The term "chemical entity", as used herein, refers to chemical compounds, complexes of at least two chemical compounds, and fragments of such compounds or complexes.

For instance, a first set of machine-readable data defining the 3-D structure of polypeptide corresponding to the Ig 1-2-3 module of NCAM or complex thereof, is combined with a second set of machine-readable data defining the structure of a chemical entity or test compound of interest using a machine programmed with instructions for evaluating the ability of the chemical entity or compound to associate with the Ig 1-2-3 module of NCAM or complex thereof and/or the location and/or orientation of such association. Such, methods provide insight into the location, orientation and energies of association of protein surfaces with such chemical entities.

The three dimensional structure defined by the data may be displayed in a graphical format permitting visual inspection of the structure, as well as visual inspection of the association of the polypeptide component(s) with an interacting compound. Alternatively, more quantitative or computational methods may be used. For example, one method of this invention for evaluating the ability of a chemical entity to associate with any of the molecules or molecular complexes set forth herein comprises the steps of: (a) employing computational means to perform a fitting operation between the chemical entity and a binding site or other surface feature of the molecule or molecular complex; and (b) analysing the results of said fitting operation to quantify the association between the chemical entity and the binding site.

This invention further provides for the use of the structural coordinates of a crystalline composition of this invention, or portions thereof, to identify reactive amino acids, such as cysteine residues, within the three-dimensional structure, preferably within or adjacent to a binding site; to generate and visualise a molecular surface, such as a water-accessible surface or a surface comprising the space-filling

van der Waals surface of all atoms; to calculate and visualise the size and shape of surface features of the protein or complex, e.g., substrate binding sites; to locate potential H-bond donors and acceptors within the three-dimensional structure, preferably within or adjacent to a ligand binding site; to calculate regions of hydrophobicity and hydrophilicity within the three-dimensional structure, preferably within or adjacent to a ligand binding site; and to calculate and visualize regions on or adjacent to the protein surface of favourable interaction energies with respect to selected functional groups of interest (e.g. amino, hydroxyl, carboxyl, methylene, alkyl, alkenyl, aromatic carbon, aromatic rings, heteroaromatic rings, etc.). One may use the foregoing approaches for characterising the polypeptide corresponding to the Ig 1-2-3 module of NCAM and its interactions with moieties of potential interacting compounds to design or select compounds capable of specific covalent attachment to reactive amino acids (e.g., cysteine) and to design or select compounds of complementary characteristics (e.g., size, shape, charge, hydrophobicity/hydrophilicity, ability to participate in hydrogen bonding, etc.) to surface features of the protein, a set of which may be preselected. Using the structural coordinates, one may also predict or calculate the orientation, binding constant or relative affinity of a given ligand to the protein in the complexed state, and use that information to design or select compounds of improved affinity.

In such cases, the structural coordinates of the polypeptide of the Ig 1-2-3 module of NCAM, or portion or complex thereof, are entered in machine readable form into a machine programmed with instructions for carrying out the desired operation and containing any necessary additional data, e.g. data defining structural and/or functional characteristics of a potential interacting compound or moiety thereof, defining molecular characteristics of the various amino acids, etc.

One method of this invention provides for selecting from a database of chemical structures a compound capable of binding to the Ig 1-2-3 module of NCAM. The method starts with structural co-ordinates of a crystalline composition of the invention, e.g., co-ordinates defining the three dimensional structure of the Ig 1-2-3 module of NCAM or a portion thereof or a complex thereof. Points associated with that three-dimensional structure are characterised with respect to the favourable ability of interactions with one or more functional groups. A database of chemical structures is then searched for candidate compounds containing one or more

functional groups disposed for favourable interaction with the protein based on the prior characterisation. Compounds having structures which best fit the points of favourable interaction with the three dimensional structure are thus identified.

It is often preferred, although not required, that such searching be conducted with the aid of a computer. In that case a first set of machine-readable data defining the 3D structure of a polypeptide corresponding to the Ig 1-2-3 module of NCAM, or a portion or polypeptide/interacting compound complex thereof, is combined with a second set of machine readable data defining one or more moieties or functional groups of interest, using a machine programmed with instructions for identifying preferred locations for favourable interaction between the functional group(s) and atoms of the polypeptide. A third set of data, i.e. data defining the location(s) of favourable interaction between polypeptide and functional group(s) is so generated. That third set of data is then combined with a fourth set of data defining the 3D structures of one or more chemical entities using a machine programmed with instructions for identifying chemical entities containing functional groups so disposed as to best fit the locations of their respective favourable interaction with the polypeptide.

Compounds having the structures selected or designed by any of the foregoing means may be tested for their ability to bind to the Ig 1-2-3 module of NCAM.

In one preferred embodiment of the invention, the compound is preferably a modulator of NCAM homophilic interaction mediated by the Ig 1-2-3 fragment. For example, a compound capable of interacting with the Ig1-2-3 homophilic binding site may be a good inhibitor of NCAM homophilic binding and NCAM function that requires this binding. Hence, compounds having the structures selected or designed by any of the foregoing means may be tested for their ability to modulate NCAM activity, such as mediation of cell differentiation and/or survival of NCAM presenting cells.

As practitioners in this art will appreciate, various computational analyses may be used to determine the degree of similarity between the three dimensional structure of a given polypeptide (or a portion or complex thereof) and a polypeptide corresponding to the Ig1-2-3 module of NCAM or complex thereof such as are

described herein. Such analyses may be carried out with commercially available software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pgs. 134-135.

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: (1) load the structures to be compared; (2) define the atom equivalences in these structures; (3) perform a fitting operation; and (4) analyse the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). Since atom equivalency within QUANTA is defined by user input, for the purpose of this invention we define equivalent atoms as protein backbone atoms (N, Cα, C and O) for all conserved residues between the two structures being compared and consider only rigid fitting operations.

When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

For the purpose of this invention, any set of structural co-ordinates of a polypeptide corresponding to Ig 1-2-3 module of NCAM or molecular complex thereof that has a root mean square deviation of conserved residue backbone atoms (N, Cα, C, O) of less than 1.5 Å when superimposed--using backbone atoms--on the relevant structural co-ordinates of a protein or complex of this invention, e.g. the co-ordinates listed in table 2, are considered identical. More preferably, the root mean square deviation is less than 1.0 Å. Most preferably, the root mean square deviation is less than 0.5 Å.

The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein from the backbone of a protein of this invention, such as a homophilic binding site of the Ig 1-2-3 module of NCAM as defined by the structural co-ordinates of table 2 and described herein.

The term "least squares" refers to a method based on the principle that the best estimate of a value is that in which the sum of the squares of the deviations of observed values is a minimum.

In order to use the structural co-ordinates generated for a crystalline substance of this invention, e.g. the structural co-ordinates set forth in table 2, it is often necessary or desirable to display them as, or convert them to, a three-dimensional shape, or to otherwise manipulate them. This is typically accomplished by the use of commercially available software such as a program, which is capable of generating three-dimensional graphical representations of molecules or portions thereof from a set of structural co-ordinates.

By way of illustration, a non-exclusive list of computer programs for viewing or otherwise manipulating protein structures include the following:
Midas (Univ. of California, San Francisco),
MidasPlus (Univ. of Cal., San Francisco)
MOIL (Univeristy of Illinois)
Yummie (Yale University)
Sybyl (Tripos, Inc.)
Insight/Discover (Biosym Technologies)
MacroModel (Columbia University)
Quanta (Molecular Simulations, Inc.)
Cerius (Molecular Simulations, Inc.)
Alchemy (Tripos, Inc.)
LabVision (Tripos, Inc.)
Rasmol (Glaxo Research and Development)
Ribbon (University of Alabama)

NAOMI (Oxford University)
Explorer Eyechem (Silicon Graphics, Inc.)
Univision (Cray Research)
Molscript (Uppsala University)
Chem-3D (Cambridge Scientific)
Chain (Baylor College of Medicine)
O (Uppsala University)
GRASP (Columbia University)
X-Plor (Molecular Simulations, Inc.; Yale Univ.)
Spartan (Wavefunction, Inc.)
Catalyst (Molecular Simulations, Inc.)
Molcadd (Tripos, Inc.)
VMD (Univ.of Illinois/Beckman Institute)
Sculpt (Interactive Simulations, Inc.)
Procheck (Brookhaven Nat'l Laboratory)
DGEOM (QCPE)
RE_VIEW (Brunel University)
Modeller (Birbeck Col., Univ. of London)
Xmol (Minnesota Supercomputing Center)
Protein Expert (Cambridge Scientific)
HyperChem (Hypercube)
MD Display (University of Washington)
PKB (Nat'l Center for Biotech. Info., NIH)
ChemX (Chemical Design, Ltd.)
Cameleon (Oxford Molecular, Inc.)
Iditis (Oxford Molecular, Inc.)

For storage, transfer and use with such programs of structural coordinates for a crystalline substance of this invention, a machine-readable storage medium is provided comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, e.g. a computer loaded with one or more programs of the sort identified above, is capable of displaying a graphical three-dimensional representation of any of the molecules or molecular complexes described herein. Machine-readable storage media comprising a data storage material include conventional computer hard

drives, floppy disks, DAT tape, CD-ROM, and other magnetic, magneto-optical, optical, floptical and other media which may be adapted for use with a computer.

Even more preferred is a machine-readable data storage medium that is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex that is defined by the structural co-ordinates of the Ig1-2-3 module of NCAM, such as the co-ordinates set forth in table 2 +/- a root mean square deviation from the conserved backbone atoms of the amino acids thereof of not more than 1.5 Å. An illustrative embodiment of this aspect of the invention is a conventional 3.5" diskette, DAT tape or hard drive encoded with a data set, preferably in PDB format, comprising the co-ordinates of table 2. FIG. 1 illustrates a print-out of a graphical three-dimensional representation of such a polypeptide.

In another embodiment, the machine-readable data storage medium comprises a data storage material encoded with a first set of machine readable data which comprises the Fourier transform of the structural co-ordinates set forth in table 2 (or again, a derivative thereof), and which, when using a machine programmed with instructions for using said data, can be combined with a second set of machine readable data comprising the X-ray diffraction pattern of a molecule or molecular complex to determine at least a portion of the structural co-ordinates corresponding to the second set of machine readable data.

Such a system may for example include a computer comprising a central processing unit ("CPU"), a working memory which may be, e.g., RAM (random-access memory) or "core" memory, mass storage memory (such as one or more disk drives or CD-ROM drives), one or more cathode-ray tube ("CRT") display terminals, one or more keyboards, one or more input lines (IP), and one or more output lines (OP), all of which are interconnected by a conventional bidirectional system bus.

Input hardware, coupled to the computer by input lines, may be implemented in a variety of ways. Machine-readable data of this invention may be inputted via the use of a modem or modems connected by a telephone line or dedicated data line. Alternatively or additionally, the input hardware may comprise CD-ROM drives or disk drives. In conjunction with the CRT display terminal, a keyboard may also be used as an input device.

Output hardware, coupled to the computer by output lines, may similarly be implemented by conventional devices. By way of example, output hardware may include a CRT display terminal for displaying a graphical representation of a protein of this invention (or portion thereof) using a program such as QUANTA as described herein. Output hardware might also include a printer, so that hard copy output may be produced, or a disk drive, to store system output for later use.

In operation, the CPU coordinates the use of the various input and output devices, co-ordinates data accesses from mass storage and accesses to and from working memory, and determines the sequence of data processing steps. A number of programs may be used to process the machine-readable data of this invention. Examples of such programs are discussed herein above. Algorithms suitable for this purpose are also implemented in programs such as Cast-3D (Chemical Abstracts Service), 3DB Unity (Tripos, Inc.), Quest-3D (Cambridge Crystallographic Data Center), and MACCS/ISIS-3D (Molecular Design Limited). These geometric searches can be augmented by steric searching, in which the size and shape requirements of the binding site are used to weed out hits that have prohibitive dimensions. Programs that may be used to synchronize the geometric and steric requirements in a search applied to the FRB of FRAP include CAVEAT (P. Bartlett, University of California, Berkeley), HOOK (MSI), ALADDIN (Daylight Software) and DOCK (http://www.cmpharm.ucsf.edu/kuntz-/kuntz.html and references cited therein). All of these searching protocols may be used in conjunction with existing corporate databases, the Cambridge Structural Database, or available chemical databases from chemical suppliers.

In one embodiment of the invention the methods involve identifying a number of compounds potentially capable of interacting with the Ig 1-2-3 module of NCAM or a fragment thereof, for example the methods may involve identification of a sub-library of compounds potentially interacting with the Ig 1-2-3 module of NCAM or fragments thereof. This may be accomplished using any conventional method. For example, all the possible members of a combinatorial library may first be enumerated, according to the available reagents and the established synthetic chemistries. Individual members may then separately be docked into a binding site of a polypeptide of MASP-2. Finally, an optimal sub-library may be selected for synthesis, based on the

ranking of their docking scores and/or diversity measures. Software for fast library enumeration has been developed, including for example CombiLibMaker in Sybyl, Analog Builder in Cerius2, and the QuaSAR-CombiGen module available in MOE (MOE Software, Chemical Computing Group, 1010 Sherbrooke Street W., Suite 910, Montreal, Canada H3A 2R7). Most of these programs can easily generate all of the 2D or 3D structures for a combinatorial library containing millions of compounds, using either fragment-based or reaction-based schemes. Other tools within these software packages are also available for decreasing the size of a virtual library prior to docking. For example, a library enumerated through CombiLibMaker can subsequently be analysed with diverse solutions (available in Sybyl) to provide a sub-library that adequately samples chemical space. QuaSAR-CombiDesign is another combinatorial library design tool available in MOE that provides a non-enumerative method for combinatorial library generation, and can, e.g. test against rule of five filters using statistical sampling techniques during library creation, creating smaller sub-libraries with user-defined property ranges. In principle, the docking step that follows library creation can be conducted using any of the available docking programs like DOCK or FlexX ©, while the diversity selection for example may be performed using software available from Daylight, Tripos (diverse solutions), or BCI or by high throughput docking as for example described by Diller and Merz.

In another example a 'divide-and-conquer' approach may be used. With this strategy, all of the product structures in a combinatorial library are viewed as having variable substituents attached through one or multiple sites on a common template. The template is first docked into the binding site and only the top-scoring poses are saved for the further consideration. Individual substituents are then independently attached onto each pose of the template, to assess which substituents can fit well into the binding site. Only those combinations of top-scoring substituents are further considered and scored to identify the whole product structures that can dock really well into the binding site. This may be done with the aid of suitable software for example PRO SELECT, CombiBUILD, CombiDOCK, DREAM ++ and FlexX ©.

In one embodiment the methods of invention comprise application of pharmacophores obtained using active site maps. Herein the term "active site" is meant to describe a site responsible of interaction with a compound and not a

catalytically active site. The method may for example be a computational approach comprising the generation of multiple, promising, structurally diverse test-compounds. The search for multiple structural series may be accomplished by coupling protein structural information with combinatorial library design using any suitable method. For example the "design in receptor" method (Murrary et al., 1999) or the method outlined herein below may be used. Methods to account for multiple protein conformations for example as described by Mason et al., 2000 may also be used, including the creation of a dynamic pharmacophore model (as for example described by Carlson et al., 2000) from molecular dynamics simulations. Also experimental and computational needle screening approaches for mapping active sites with molecular fragments may be used for example as described in Boehm et al., 2000. Any suitable software tools for mapping site points (e.g. GRID and SITEPOINT) may be used with the invention. Also MCSS techniques for generating site maps may be used.

Suitable methods may for example comprise generation of active site maps from protein structures. Then all possible 2-, 3- and 4-point pharmacophores can be enumerated from the site map and encoded as a bit string (signature) these pharmacophores define a space to be probed by compounds that are selected using the informative library design tool. The metric used to evaluate the success of the approach is the number of active scaffolds selected in the library design, with the number of active compounds as a secondary measure. Any suitable algorithm for site map generation may be used, for example algorithms generating between 10 and 80 feature positions for each active site. An example of such a method is described for example by Eksterowicz et al J Mol Graph Model. 2002 Jun;20(6):469-77.

Information of the various binding sites of the Ig1-2-3 module along with the crystal structure of the invention provide a tool for the examination of the biological significance of the observed Ig1-to-Ig2, Ig1-to-Ig3, and Ig2-to-Ig3 contacts, and for the screening for compounds capable of mimicking the binding of the Ig1-to-Ig2, Ig1-to-Ig3, Ig3-to-Ig1, Ig2-to-Ig3 and Ig2-to-Ig2 modules of NCAM.

Screening assay

It is an important objective of the present invention to provide an assay for selecting a compound capable of modulating cell differentiation and/or survival of NCAM presenting cells, said compound being her and below termed "the candidate compound", comprising the steps of

i) incubating in vitro at least one candidate compound, and a second compound, wherein said second compound is the Ig1-2-3 module of NCAM, or fragments thereof, such as the Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules in a solution;

ii) preparing a crystal of a complex of the candidate compound of (i) and the compound of (ii) by co-crystallisation, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of said second compound or a complex of the second with the fist compound to a resolution at most 5. 0 Å, preferably at most 4. 0 Å, more preferably at most 3. 0 Å, even more preferably at most 1. 5 Å,

iii) determining the three-dimensional structure of the crystal of step (ii) followed by

iv) the selection of a candidate compound capable of (1) interacting with the Ig1 module and thereby modulating the interaction between the Ig3 and Ig1 module in the crystal of the Ig1-2-3 module of NCAM, and/or (2) interacting with the Ig3 module and thereby modulating the interaction between the Ig1 and the Ig3 module in the crystal of the Ig1-2-3 module of NCAM, and/or (3) interacting with the Ig2 module and thereby modulating the interaction between the Ig3 and Ig2 module in the crystal of the Ig1-2-3 module of NCAM and/or (4) interacting with the Ig3 module and thereby modulating the interaction between the Ig2 and Ig3 module in the crystal of the Ig1-2-3 module of NCAM , and/or (5) interacting with the Ig2 module and thereby modulating the interaction of the Ig2 and Ig2 module in the crystal of the Ig1-2-3 module of NCAM;

v) contacting in vitro the candidate compound of step (iv) with a cell expressing NCAM followed by

vi) evaluating the cellular response.

In one embodiment the step ii) of the above assay may comprise soaking a crystal of the second compound with a candidate compound instead of crystallising of a complex of the candidate and second compound by co-crystallisation.

A model of the Ig1-2-3 crystalline module of NCAM

The identification of a new compound capable of modulating cell differentiation and/or survival of NCAM presenting cells may in one aspect of the invention be performed by screening a computer model template, such as a three-dimensional crystal structure of the individual modules of NCAM. Accordingly, the invention also relates to providing a screening method for selecting a compound capable of modulating cell differentiation and/or survival of NCAM presenting cells, comprising the steps of

i) providing a polypeptide comprising the Ig1-2-3 module of NCAM:

ii) generating a structural model of the Ig1-2-3 module of NCAM, or fragments of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules by computer modelling techniques;

iii) designing a compound into the structure of said generated model of step i);

iv) testing the compound of step (ii) in an in vitro or in vivo assay.

The above screening method may in one embodiment of the invention comprise a computer generated model of the Ig1-2-3 module of NCAM, or fragments of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules in a solution. Such a model may be generated on the basis of the data obtained, for example, from Nuclear Magnetic Resonance spectroscopy of the samples of the above modules. Alternatively, in another embodiment a computer generated model may be a structural model of a crystal of the above modules.

In a preferred embodiment of the invention a computer generated structural structure model of the Ig1-2-3 module for screening a compound capable of modulating NCAM-dependent cell survival and differentiation is provided.

Designing interacting compounds

Designing interacting compounds

Generating a site map

Feature points complementary to the active site are computed using an internally developed software tool. For example, a hydrogen bond donor feature is mapped in

the proximity of a hydrogen bond acceptor in the protein active site. The collection of 3D coordinates and labels (acceptors, donors, negatives, positives, hydrophobes and aromatics) is called a site map. Technically, the site map is the union of three separately computed maps, ESMap which contains the electrostatic feature points (P, N, and H) HBMap with hydrogen-bonding feature points (D and A) and AroMap containing aromatic feature points (Ar).

The electrostatic feature map, ESMap, is computed by first using the sphere placement algorithm employed in the program PASS (Brady et al., 2000). It generates an evenly-distributed setof points (ProbeMap) in regions of buried volume along the protein surface. A subset of points in the ProbeMap comprises the P, N, and H feature points depending upon the local electrostatic character of the protein. The CVFF molecular mechanics force field is used to compute the electrostatic potential, φi , at each point *i* of ProbeMap, along with the mean potential φ and mean magnitude $|\varphi|$ averaged over all points in ProbeMap. The value of φi determines whether or not point *i* is included as a P, N, or H feature point, according to the following definitions

$i>\varphi+1.5*\sigma(\varphi)$, i=N feature point

$i>\varphi-1.5*\sigma(\varphi)$, i=P feature point

$|\varphi|-1.0*\sigma(|\varphi|)<|\varphi i|<(|\varphi|)+1.0*\sigma(|\varphi|)$, i=H feature point

Here $\sigma(X)$ denotes the standard deviation about the mean of quantity X. This normalizes the point assignments relative to the overall electrostatic environment of the active site. This presents non charge-neutral protein structures (which may result from counter ions not being resolved or present in the crystal structures) from skewing feature point assignments unreasonably.

The hydrogen-bonding feature map, HBMap, is determined by projecting complementary points outward from known hydrogen-bonding atoms of the protein. The resulting superset of points is filtered on the basis of steric clash, insufficient burial and minimal proximity of alike feature points. Ideal hydrogen-bonding points are positioned on the basis of the mean angle and distance as observed in the PDB (see for example table 2). Points that clash with the protein are removed. However, for robustness, small positional perturbations are applied to retain potentially important hydrogen-bonding positions. Bifurcated hydrogen-bonding joints are

computed heuristically by investigating full rings of points equally bifurcated between protein atoms that are considered moderate or strong hydrogen bond participants. Points on such rings are retained as bifurcated HB points if they do not violate steric clash, burial and mutual proximity conditions. To build the final HBMap, the surviving sets of ideal and bifurcated HB points are combined and subjected to filtration on the basis of mutual proximity.

The AroMap set of aromatic feature points is computed by repeatedly docking a benzene ring into the protein active site and retaining the centroids of the top-scoring configurations. The protein is represented using a polar-hydrogen CVFF force field. The docking is performed using internal code in local optimization mode. One hundred separate local docking trials with different starting positions are performed. Any of the docked configurations whose score lies within an energy window of 5 kcal/mol of the minimum-energy configuration is included in AroMap. Again points are subjected to filtration on the basis of burial and mutual proximity.

Converting pharmacophores into a signature

Pharmacophores are generated on the basis of feature points in the active site by exhaustive enumeration of all 2-,3-, and 4-point subsets of the feature points. For all pairs of feature points their distance in 3D-space is precomputed. In order to arrive at a discrete representation of a pharmacophore, the distances are binned, applying a user-defined binning scheme. Chirality is denoted by encoding the handedness of 4-point pharmacophores. Each pharmacophore is mapped onto a unique address, such that any possible combination of up to four features and distances is represented. The address is taken for a binary representation of the pharmacophores; called a signature. The length of the signature is the highest possible address for an encoding of a 4-point pharmacophore. All bits in the signature are initially set to 0. In order to represent a pharmacophore the bit at the respective address in the signature is turned on (set to 1). For the representation of the active site all pharmacophores are exhaustively enumerated and the respective bits are turned on.

Union of signatures for multiple structures

Multiple signatures may be combined. The binary union of multiple signatures yields a single bit string representing all pharmacophores present in any structure. Any

consensus threshold *c* can be used to define the consensus representation of multiple active sites. That is, a pharmacophore is present in at least *c* of active site conformations. Note that this way of handling multiple active site snapshots is quite expedient.

Molecular signatures

Test compounds are encoded as follows. First, conformers are generated for each compound using an internal tool that generates a fairly complete conformational model of the molecule. Features are assigned using a substructure-based set of rules. Pharmacophores are enumerated from these three-dimensional feature positions following the same protocol as for the active site, thus ensuring compatibility of the binary encodings. However, multiple conformers need to be represented simultaneously here. This is done by wrapping the exhaustive enumeration of pharmacophores for a single conformer into an extra loop over all the conformers of a compound. That is, any pharmacophore on any conformer of a compound is represented by turning the respective bit in the signature on.

Molecular signature masking

With the binary representation of the active site and the binary representation of the molecules being defined analogously, the meaning of a bit at a certain address is the same (the same pharmacophore, within the tolerances of the distance binning). Therefore, representing a design space amounts to masking all molecule signatures by the active site signature. Masking a signature means taking the logical *and* of the bits of the site signature and the molecule signature. For a given molecule, bits representing pharmacophores not present in the active site are turned off, whereas the bits of the pharmacophores in the active site can be either on or off, depending on their presence or absence in the molecules. This way only the pharmacophore space defined by the active site is taken into account.

Informative library design

Informative library design is a molecule selection strategy that optimises information return for a given virtual library. The goal is to detect a set of features (pharmacophores) that determine activity against a particular test compound. Informative design aims at selecting a set of compounds such that the resulting subset will interrogate the test compound in different, but overlapping ways.

Molecules are selected for synthesis and screening such that each pharmacophore in the design space has a unique pattern of occurrence in the molecules of the set. This unique 'code' enables the identification and retention of the important pharmacophores when the set of compounds is assayed, regardless of the actual experimental outcome. This is in contrast to diversity methods that seek to produce a unique pattern of pharmacophore occurrences in each molecule.

Given a design space, the algorithm seeks to optimize decoding as many pharmacophores as possible, with the smoothest distribution across the size of pharmacophore classes. A pharmacophore class refers to the subset of pharmacophores that all have the same code or pattern. Note that the optimum solution is a set of compounds that enables decoding each individual pharmacophore. However, this may not be possible due either to the source pool, bit correlation or to limited size of selection. The cost function for an unconstrained optimisation in terms of molecule selection is the entropy of the class distribution. The entropy is given by

$$H = -\sum_{i=1}^{c} \frac{|Ci|}{f} \ln \frac{|Ci|}{f}$$

where H is the entropy of the feature classes, C the number of distinct classes, f the number of features in the design space and $|c|$ is the size of class i. During the course of the optimisation, molecules are selected, such as to maximize H.

Compound

By the term "candidate compound" in the present context is meant a compound capable of

i) interacting with the Ig1 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) interacting with the Ig2 module of NCAM, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iv) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

v) interacting with the Ig2 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules,

and thereby modulating cell differentiation and survival mediated by NCAM homophylic binding.

A preferred candidate compound according to the invention is selected in the above described screening assay or screening method(s).

Thus, the present invention provides in one embodiment a compound having the amino acid sequence WFSPNGEKLSPNQ set forth in SEQ ID NO: 1, fragments or variants thereof.

In another embodiment a compound of the invention is having the amino acid sequence YKCVVTAEDGTQSE set forth in SEQ ID NO: 2, fragments or variants thereof.

In still another embodiment the invention provides a compound having the amino acid sequence TLVADADGFPEP set forth in SEQ ID NO: 3, fragments or variants thereof.

In yet another embodiment the invention provides a compound having the amino acid sequence QIRGIKKTD set forth in SEQ ID NO: 4, fragments or variants thereof.

In still yet another embodiment the invention provides a compound having the amino acid sequence DVR set forth in SEQ ID NO: 5, fragments or variants thereof.

Yet in another embodiment the compound of the invention is having the amino acid sequence RGIKKTD set forth in SEQ ID NO: 6, fragments or variants thereof.

In yet a further embodiment the invention provides a compound is having the amino acid sequence DVRRGIKKTD set forth in SEQ ID NO: 7, fragments or variants thereof.

Another aspect of the invention concerns a compound is having the amino acid sequence KEGED set forth in SEQ ID NO: 8, fragments or variants thereof.

In yet another aspect a compound is having the amino acid sequence IRGIKKTD set forth in SEQ ID NO: 9, fragments or variants thereof.

The invention further provides a compound having the amino acid sequence KEGEDGIRGIKKTD set forth in SEQ ID NO: 10, fragments or variants thereof.

Moreover, in another embodiment the invention provides a compound having the amino acid sequence DKNDE set forth in SEQ ID NO: 11, fragments or variants thereof.

In still another embodiment the invention concerns a compound having the amino acid sequence TVQARNSIVNAT set forth in SEQ ID NO: 12, fragments or variants thereof.

In yet another embodiment of the invention the compound is having the amino acid sequence SIHLKVFAK set forth in SEQ ID NO: 13, fragments or variants thereof.

In yet another embodiment the compound is having the amino acid sequence LSNNYLQIR set forth in SEQ ID NO: 14, fragments or variants thereof.

In a further embodiment the invention provides a compound having the amino acid sequence RFIVLSNNYLQI set forth in SEQ ID NO: 15, fragments or variants thereof.

Further, in yet another embodiment the invention provides a compound having the amino acid sequence KKDVRFIVLSNNYLQI set forth in SEQ ID NO: 16, fragments or variants thereof.

Furthermore, in yet another embodiment the invention provides a compound having the amino acid sequence QEFKEGEDAVIV set forth in SEQ ID NO: 17, fragments or variants thereof.

The invention further provides a compound having the amino acid sequence KEGEDAVIVCD set forth in SEQ ID NO: 18, fragments or variants thereof.

The identified above sequences according to the invention represent different fragments a homophylic binding site of NCAM in the Ig1-2-3 module and are capable of modulation of differentiation and/or survival of an NCAM-presenting cell.

Accordingly, the sequences identified above may be used for the manufacture of a medicament for the treatment of a condition or disease wherein the modulation of NCAM homophtlic interaction would lead to improvement or rescue.

Use of the Ig1-2-3 module of NCAM

In an important aspect of the invention the Ig1-2-3 module of NCAM is used for the manufacture of a kit for screening a candidate compound of the invention. The candidate compound is capable of modulating NCAM-dependent cell differentiation and/or survival. This means that the Ig1-2-3 module may be applied in a commercial kit to be used for screening potential compound candidates.

Kit

According to the invention the kit is for screening a candidate compound capable of modulating NCAM-dependent cell differentiation and/or survival. The kit of the invention may comprise

i) the Ig1-2-3 module of NCAM, or fragments thereof, such as the Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules, in a solution;

ii) a solution of the module(s) according to (i),

iii) a crystal of the Ig1-2-3 module of NCAM,

In one embodiment the kit of the invention may comprise a solution of the labelled Ig1-2-3 module of NCAM, or fragments thereof, such as the Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules, The modules may be conjugated with the horse radish peroxidase, alkaline phospatase, streptavidin, avidin, biotin or an antibody to said modules, or fragments of the antibody. In another embodiment the kit may comprise a solution of the above modules, wherein said modules are containing a radioactive label, such as for example N^{15}.

Pharmaceutical composition

Once the candidate compound of the invention has been identified it is further within the scope of the invention to provide a pharmaceutical composition comprising one or more of the compounds as defined above. In the present context the term pharmaceutical composition is used synonymously with the term medicament.

The scope of the invention is further related to a pharmaceutical composition capable of preventing death of cells *in vitro* or *in vivo*, wherein the composition is administered to a subject, *in vitro* or *in vivo* in an effective amount of one or more of the compounds described above or a composition as described below, so as to promote cell differentiation and modulation of proliferation of neural cells and neuronal plasticity, and stimulation of survival and regeneration of NCAM presenting cells and/or NCAM ligand presenting cells in several tissues and organs as discussed herein. The medicament of the invention comprises an effective amount of one or more of the compounds as defined above, or a composition as defined above in combination with pharmaceutically acceptable additives. Such medicament may suitably be formulated for oral, percutaneous, intramuscular, intravenous, intracranial, intrathecal, intracerebroventricular, intranasal or pulmonal administration.

The present invention further concerns a medicament for the treatment of diseases and conditions of the central and peripheral nervous system, of the muscles or of various organs, wherein said medicament comprises an effective amount of one or more of the compounds as defined above or a composition as defined above in combination with pharmaceutically acceptable additives or carriers. Such medicament may suitably be formulated for oral, percutaneous, intramuscular,

intravenous, intracranial, intrathecal, intracerebroventricular, intranasal or pulmonal administration.

Formulation

Strategies in formulation development of medicaments and compositions based on the compounds of the present invention generally correspond to formulation strategies for any other protein-based drug product. Potential problems and the guidance required to overcome these problems are dealt with in several textbooks, e.g. "Therapeutic Peptides and Protein Formulation. Processing and Delivery Systems", Ed. A.K. Banga, Technomic Publishing AG, Basel, 1995.

Injectables are usually prepared either as liquid solutions or suspensions, solid forms suitable for solution in, or suspension in, liquid prior to injection. The preparation may also be emulsified. The active ingredient is often mixed with excipients, which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are for example water, saline, dextrose, glycerol, ethanol or the like, and combinations thereof. In addition, if desired, the preparation may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, which enhance the effectiveness or transportation of the preparation.

Formulations of the compounds of the invention can be prepared by techniques known to the person skilled in the art. The formulations may contain pharmaceutically acceptable carriers and excipients including microspheres, liposomes, microcapsules, nanoparticles or the like.

Administration

For most indications a localised or substantially localised application is preferred. The compounds are in particular used in combination with a prosthetic device such as a prosthetic nerve guide. Thus, in a further aspect, the present invention relates to a prosthetic nerve guide, characterised in that it comprises one or more of the compounds or the composition defined above. Nerve guides are known in the art.

The preparation may suitably be administered by injection, optionally at the site, where the active ingredient is to exert its effect. Additional formulations which are

suitable for other modes of administration include suppositories, nasal, pulmonal and, in some cases, oral formulations. For suppositories, traditional binders and carriers include polyalkylene glycols or triglycerides. Such suppositories may be formed from mixtures containing the active ingredient(s) in the range of from 0.5% to 10%, preferably 1-2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and generally contain 10-95% of the active ingredient(s), preferably 25-70%.

Other formulations are such suitable for nasal and pulmonal administration, e.g. inhalators and aerosols.

The active compound may be formulated as neutral or salt forms. Pharmaceutically acceptable salts include acid addition salts (formed with the free amino groups of the peptide compound) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic acid, oxalic acid, tartaric acid, mandelic acid, and the like. Salts formed with the free carboxyl group may also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

The preparations are administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective. The quantity to be administered depends on the subject to be treated, including, e.g. the weight and age of the subject, the disease to be treated and the stage of disease. Suitable dosage ranges are of the order of several hundred µg active ingredient per administration with a preferred range of from about 0.1 µg to 100 mg, such as in the range of from about 1 µg to 100 mg, and especially in the range of from about 10 µg to 50 mg. Administration may be performed once or may be followed by subsequent administrations. The dosage will also depend on the route of administration and will vary with the age and weight of the subject to be treated. A preferred dosis would be in the interval 0.5 mg to 50 mg per 70 kg body weight.

Some of the candidate compounds of the present invention are sufficiently active, but for others, the effect will be enhanced if the preparation further comprises pharmaceutically acceptable additives and/or carriers. Such additives and carriers will be known in the art. In some cases, it will be advantageous to include a compound, which promote delivery of the active substance to its target.

In another embodiment it may be advantageous to administer the candidate compound(s) according to the invention with other substances to obtain a synergistic effect. Examples of such other substances may be a growth factor, which can induce differentiation, or a hormone, or a transplant of cells, including a transplant of stem cells, or gene therapy, or immuno-therapy.

In many instances, it will be necessary to administrate the formulation multiple times. Administration may be a continuous infusion, such as intra-ventricular infusion or administration in more doses such as more times a day, daily, more times a week, or weekly. It is preferred that administration of the medicament is initiated before or shortly after the individual has been subjected to the factor(s) that may lead to cell death. Preferably the medicament is administered within 8 hours from the factor onset, such as within 5 hours from the factor onset. Many of the compounds exhibit a long-term effect whereby administration of the compounds may be conducted with long intervals, such as 1 week or 2 weeks.

In one embodiment of the invention the administration of the present compound may be immediately after an acute injury, such as an acute stroke, or at the most 8 hours after said stroke in order for the present compound to have a stimulatory effect on cell survival. Further, in cases concerning proliferation and/or differentiation the administration according to the invention is not time dependent, i.e. it may be administered at any time.

Producing a pharmaceutical

In another aspect the invention relates to a process of producing a pharmaceutical composition, comprising mixing an effective amount of one or more of the compounds of the invention, or a pharmaceutical composition according to the invention with one or more pharmaceutically acceptable additives or carriers, and administer an effective amount of at least one of said compound, or said

pharmaceutical composition to a subject.

In yet a further aspect the invention relates to a method of treating an individual suffering from one or more of the diseases discussed above by administering the said individual a compound as described herein or a pharmaceutical composition comprising said compound.

Medicament

The candidate compounds of the invention may be used in the manufacture of medicaments to be used to treat conditions effecting the peripheral and/or the central nervous system and/or muscles and other tissues expressing NCAM or NCAM ligands as well as other conditions in which a stimulation of NCAM function or the function of a NCAM ligand is beneficial.

Furthermore, the candidate compound of the invention may be for the manufacture of a medicament for treatment of normal, degenerated or damaged NCAM and/or NCAM ligand presenting cells.

In particular the compound and/or pharmaceutical composition of the invention may be used in the treatment of clinical conditions, such as Neoplasms such as malignant neoplasms, benign neoplasms, carcinoma in situ and neoplasms of uncertain behavior, diseases of endocrine glands, such as diabetes mellitus, psychoses, such as senile and presenile organic psychotic conditions, alcoholic psychoses, drug psychoses, transient organic psychotic conditions, Alzheimer's disease, cerebral lipidoses, epilepsy, general paresis [syphilis], hepatolenticular degeneration, Huntington's chorea, Jakob-Creutzfeldt disease, multiple sclerosis, Pick's disease of the brain, syphilis,Schizophrenic disorders, affective psychoses, neurotic disorders, personality disorders, including character neurosis, non-psychotic personality disorder associated with organic brain syndromes, paranoid personality disorder, fanatic personality, paranoid personality (disorder), paranoid traits, sexual deviations and disorders, mental retardation, disease in the nervous system and sense organs, cognitive anomalies, inflammatory disease of the central nervous system, such as meningitis, encephalitis, cerebral degenerations, such as Alzheimer's disease, Pick's disease, senile degeneration of brain, communicating hydrocephalus, obstructive hydrocephalus, Parkinson's disease including other

extra pyramidal disease and abnormal movement disorders, spino-cerebellar disease, cerebellar ataxia, Marie's, Sanger-Brown, Dyssynergia cerebellaris myoclonica, primary cerebellar degeneration, such as spinal muscular atrophy, familial, juvenile, adult spinal muscular atrophy, motor neuron disease, amyotrophic lateral sclerosis, motor neuron disease, progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis, other anterior horn cell diseases, anterior horn cell disease, unspecified, other diseases of spinal cord, syringomyelia and syringobulbia, vascular myelopathies, acute infarction of spinal cord (embolic) (nonembolic), arterial thrombosis of spinal cord, edema of spinal cord, subacute necrotic myelopathy, subacute combined degeneration of spinal cord in diseases classified elsewhere, myelopathy, drug-induced, radiation-induced myelitis, disorders of the autonomic nervous system, disorders of peripheral autonomic, sympathetic, parasympathetic, or vegetative system, familial dysautonomia [Riley-Day syndrome], idiopathic peripheral autonomic neuropathy, carotid sinus syncope or syndrome, cervical sympathetic dystrophy or paralysis. peripheral autonomic neuropathy in disorders classified elsewhere, amyloidosis, diseases of the peripheral nerve system, brachial plexus lesions, cervical rib syndrome, costoclavicular syndrome, scalenus anterior syndrome, thoracic outlet syndrome, brachial neuritis or radiculitis, including in newborn; inflammatory and toxic neuropathy, including acute infective polyneuritis, Guillain-Barre syndrome, Postinfectious polyneuritis, polyneuropathy in collagen vascular disease, disorders affecting multiple structures of eye, purulent endophthalmitis, diseases of the ear and mastoid process, chronic rheumatic heart disease, ischaemic heart disease, arrhythmia, diseases in the pulmonary system, abnormality of organs and soft tissues in newborn, including in the nerve system, complications of the administration of anesthetic or other sedation in labor and delivery, diseases in the skin including infection, insufficient circulation problem, injuries, including after surgery, crushing injury, burns. Injuries to nerves and spinal cord, including division of nerve, lesion in continuity (with or without open wound), traumatic neuroma (with or without open wound), traumatic transient paralysis (with or without open wound), accidental puncture or laceration during medical procedure, injury to optic nerve and pathways, optic nerve injury, second cranial nerve, injury to optic chiasm, injury to optic pathways, injury to visual cortex, unspecified blindness, injury to other cranial nerve(s), injury to other and unspecified nerves. Poisoning by drugs, medicinal and biological substances, genetic or traumatic atrophic muscle disorders; or for the

treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas, such as diabetes mellitus type I and II, of the kidney, such as nephrosis.

Conditions of CNS/PNS

In another aspect of the invention the compounds are for the treatment of diseases or conditions of the central and peripheral nervous system, such as postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart and bowel, and for the treatment of postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression.

Preventing cell death

Further, the candidate compounds according to the invention may be used for preventing cell death of cells being implanted or transplanted. This is particularly useful when using compounds having a long-term effect.

In another aspect of the invention the candidate compounds may be synthesised and secreted from implanted or injected gene manipulated cells.

Heart muscles

Furthermore, the candidate compound and/or pharmaceutical composition may be

for preventing cell death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis. Furthermore, in one embodiment the compound and/or pharmaceutical composition is for the stimulation of the survival of heart muscle cells, such as survival after acute myocardial infarction. In another aspect the compound and/or pharmaceutical composition is for re-vascularisation, such as after injuries.

Memory

In another aspect the candidate compound and/or pharmaceutical composition is used for stimulation of the ability to learn and/or of the short and/or long-term memory.

Regeneration

In one aspect of the invention treatment by the use of the candidate compounds according to the invention is useful for the stimulation of regenerating cells which are degenerating or at risk of dying due to a variety of factors, such as traumas and injuries, acute diseases, chronic diseases and/or disorders, in particular degenerative diseases normally leading to cell death, other external factors, such as medical and/or surgical treatments and/or diagnostic methods that may cause formation of free radicals or otherwise have cytotoxic effects, such as X-rays and chemotherapy.

For wound-healing

It is also within the scope of the invention to use the candidate compound and/or pharmaceutical composition for the promotion of wound-healing. The present compounds are capable of interfering with cell adhesion and thereby promote the wound healing process.

Cancer

The invention further discloses the use of the candidate compound and/or pharmaceutical composition in the treatment of cancer. NCAM regulates motility and inhibits cancer cells from spreading.

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Experimentals

The following is a non-limiting description of the production of the second compound of the invention, comprising NCAM Ig1-2-3 module or fragments thereof, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3.

Production of the Ig1-2-3 and Ig3 fragments of NCAM

The NCAM Ig1-2-3 and Ig3 fragments were produced as recombinant proteins in the yeast *P. pastoris* expression system (Invitrogen). The cDNA fragments encoding Ig1-2-3 and Ig3 of rat NCAM (NCBI accession number NP_113709), corresponding to residues 1-289 and 191-289, respectively, were synthesized by PCR using rat NCAM cDNA as a template. The following DNA primers were used for cloning of Ig1-2-3 and Ig3, respectively: upper (5'-TCT CTC GAG TTC TGC AGG TAG ATA TTG TT-3') (SEQ ID NO: 37) and lower (5'-AAA CCC GGG TTA CTT TGC AAA GAC CTT-3') (SEQ ID NO: 30), upper (5'-GAA TAC GTA ACT GTC CAG GCC AGA C-3') (SEQ ID NO: 31) and lower (5'-AAA CCT AGG TTA CTT TGC AAA GAC CTT G-3') (SEQ ID NO: 32). The amplified cDNA fragments were subcloned into the pHIL-S1 and the pPIC9K plasmids (Invitrogen), respectively. The recombinant plasmids were linearized with the NsiI and SacI restriction enzymes, respectively, and used for transformation of the *P. pastoris* strain His 4 GS-115 (Invitrogen). Large-scale production of the recombinant proteins was performed employing a high-density feed-batch fermentation technique in a Biostat B fermentor (B. Braun Biotech Int. GmbH). Ig1-2-3 and Ig3 were purified from concentrated and desalted medium by anion-exchange chromatography on a HiTrap Q-Sepharose 5 ml column (Pharmacia),

followed by gel filtration chromatography on a HiLoad 16/60 Superdex-75 column (Pharmacia). The Ig1-2-3 was enzymatically deglycosylated with PNGase-F endo-N-glycosidase (New England Biolabs) at 37 °C in PBS buffer pH 7.4. The authenticity of the protein fragments was confirmed by DNA sequencing of the recombinant plasmids, by amino acid sequencing of the 10-12 N-terminal residues, and by MALDI-TOF MS. The recombinant Ig1-2-3 and Ig3 fragments contained respectively two (RV) and five (EAEAY) additional N-terminal residues from the cloning vector. The purity of the proteins was at least 95% as estimated by SDS-PAGE.

Production of the Ig1-2-3 and Ig3 mutants

An Ig1-2-3 mutant (Ig1-2-3mut) containing the substitutions E11A, E16A, and K18A was produced as a recombinant protein in the yeast *P. pastoris* expression system following the procedure described for the Ig1-2-3 fragment. The three mutations were introduced by PCR using the following DNA primer: upper (5'-CTG CAG GTA GAT ATT GTT CCC AGC CAA GGA GCC ATC AGC GTT GGA GCC TCC GCC TTC TTC CTG TGT CAA GTG GCA-3') (SEQ ID NO: 33).

Two Ig3 mutants containing the substitutions: R198A, D249G, E287A (Ig3mut1) and K285A, F287A (Ig3mut2) were produced as recombinant proteins in the yeast *P. pastoris* expression system following the procedure described for the Ig3 fragment. Mutations were introduced by PCR using the following DNA primers: upper1 (5'-AAA TAC GTA ACT GTC CAG GCC GCC CAG AGC ATC GTG-3') (SEQ ID NO: 38), upper2 (5'-GGC GAC AGT TCG GCG TTA ACC ATC AGG AAT GTG GAC-3') (SEQ ID NO: 34), and lower (5'-GGT TAA CGC CGA ACT GTC GCC ACT GAA GAT GTG CTT CTC-3') (SEQ ID NO: 35) for Ig3mut1; and lower (5'-AAA CTT AGG TTA CTT TGC TGC GAC TGC GAG GTG GAT GGA GGC ATC-3') (SEQ ID NO: 36) for Ig3mut2. The DNA constructs of Ig1-2-3mut, Ig3mut1, and Ig3mut2 were verified by DNA sequencing. Folding of the Ig3 module and its mutants, as well as presence of carbohydrates, was confirmed by one-dimensional proton NMR spectra recorded at 800 MHz on a Varian NMR spectrometer (Varian Inc.) at 25°C in PBS buffer pH 7.4.

Preparation of peptides

Peptides were synthesized using the 9-fluorenylmethoxycarbonyl (Fmoc) protection strategy on a TentaGel resin (Rapp Polymere) using Fmoc protected amino acids (Calbiochem-Novabiochem). Peptides were at least 85% pure as estimated by

MALDI-TOF MS. All peptides were synthesized with free NH_2 and carboxy-amidated COOH groups.

Crystallization and data collection

Crystals of NCAM Ig1-2-3 were grown at 18°C using the hanging-drop vapor diffusion method, with drops of equal volumes of reservoir and protein solutions (4 mg ml^{-1} in 5 mM Na phosphate, 150 mM NaCl, pH 7.4). The reservoir solution contained 14-17% w/v PEG 4000, 450 mM Li sulfate, 100 mM Na acetate, pH 5.2. The crystals belong to space group $I2_12_12_1$ with one molecule in the asymmetric unit and cell dimensions of a = 51.5, b = 108.5, and c = 149.0 Å. The crystals were flash cooled in liquid nitrogen using 15% v/v glycerol as cryoprotectant. Two data sets were collected on the same crystal. The high-resolution data were collected to 2.0 Å at 120 K at beamline I711, Max-Lab, Lund, Sweden, and the low-resolution data were collected to 3.5 Å at 120 K on a Rigaku RU300 rotating anode equipped with a MAR345 image plate detector. The data sets were combined and processed with DENZO/SCALEPACK (Otwinowski and Minor, 1997) and the CCP4 suite of programs (Collaborative Computational Project No. 4, 1994).

Structure determination and refinement

The structure was determined by molecular replacement with the programs AmoRe (Navaza and Saludjan, 1997) and CNS version 1.0 (Brünger et al., 1998), using the X-ray structures of the Ig2 and Ig1 modules of NCAM (Kasper et al., 2000) as search models. Initially, the position of the Ig2 module was located using AmoRe. The Ig1 module was subsequently located using CNS. An electron density map was calculated based on phase information from Ig1 and Ig2. Residues of Ig3 were gradually built into this map. Map interpretation and model building were carried out using the program O (Jones et al., 1991). After several building and refinement cycles, ARP/wARP version 5.1 (Perrakis et al., 1999) was used to rebuild 233 out of 291 residues of NCAM Ig1-2-3. CNS was used to carry out the final rounds of refinements. The final model contains amino acids (-1)-238 and 241-289, and 266 water molecules. Amino acids are numbered according to the mature sequence of NCAM. Residues Arg and Val originating from the cloning site were given negative integers -2 and -1, respectively. Using all reflections in the resolution range 50-2.0 Å, the R_{cryst} is 21.8% and the R_{free} is 23.8% (3% test set, corresponding to 828 reflections). Data collection and refinement statistics are given in Table 1.

Interdomain geometry was determined according to Bork et al. (1996), and buried accessible surface areas were calculated using the Protein-Protein Interaction Server (http://www.biochem.ucl.ac.uk/bsm/PP/server) (Jones and Thornton, 1996). Figures were prepared with the programs MOLSCRIPT, RASTER3D (Kraulis, 1991; Merritt and Bacon, 1997), and Insight II (Accelrys).
The atomic coordinates of the structure is demonstrated in the Table 2.

Protein Data Bank ID code
The coordinates of the structure have been deposited with the Protein Data Bank under ID code 1QZ1.

Cell culture and immunostaining
The NCAM-expressing pheochromocytoma PC12-E2 cell line (Wu and Bradshaw, 1995) was a gift from Dr. Klaus Seedorf, Hagedorn Research Institute, Denmark. The cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 5% v/v fetal calf serum (FCS) and 10% v/v horse serum (HS), 100 U ml^{-1} penicillin, 100 µg ml^{-1} streptomycin (all from Gibco BRL) at 37°C in a humidified atmosphere containing 5% CO_2. The fibroblastoid mouse cell line, L929 (European Cell Culture Collection), was stably transfected with the eukaryotic expression vector pHβ-Apr-1-neo (Gunning et al., 1987) containing a full-length cDNA encoding human 140 kDa NCAM-B or the vector alone. The NCAM cDNA did not contain the exons VASE, a, b, c, or AAG. The cells were routinely grown at 37°C, 5% CO_2 in DMEM supplemented with 10% v/v FCS, 100 U ml^{-1} penicillin, and 100 µg ml^{-1} streptomycin. For analysis of neurite outgrowth, PC12-E2 cells (8,000 cells per well) were seeded on top of a confluent monolayer of transfected fibroblastoid L929 cells in four-well LabTek Tissue Culture Chamber Slides (NUNC). The cells were grown for 24 h in DMEM supplemented with 1% v/v HS, before analysis. The glycosylated recombinant rat Ig3 module of NCAM (wildtype and mutated forms) or selected peptides were added immediately after seeding of PC12-E2 cells in order to evaluate their inhibitory effects on adhesion, as reflected by interference with NCAM-mediated neurite outgrowth. Ig3wt, Ig3mut1, and Ig3mut2 were tested at a concentration of 500 □g ml^{-1}. All peptides were tested at a concentration of 200 □g ml^{-1}. Proper controls were included and the person performing the experiments did not know the identity of the mutants or peptides.

To evaluate the length of processes of PC12-E2 cells, the co-cultures were fixed in 4% w/v paraformaldehyde for 25 min. After washing in PBS, cells were blocked with 10% v/v goat serum (DAKO) for 30 min and subsequently incubated for 1 h at room temperature with a mouse monoclonal anti-Thy-1 antibody (Caltag Laboratories) (1:100 in PBS containing 10% v/v goat serum). After washing, cells were incubated for 1 h at room temperature with Alexa-Fluor 568™ goat anti-mouse IgG (Molecular Probes) (1:1000 in PBS containing 10% goat serum). All washes were performed for 10 min in PBS, and repeated three times.

The total neurite length per cell was analyzed using the software ProcessLength (Rønn et al., 2000). Five independent experiments with the Ig3 module, its mutants, and the individual peptides were performed. In each experiment neurites from 200-300 cells were analyzed. In order to compare results of individual experiments and due to the inherently high variability of cell experiments, the data were normalized setting the difference between the average neurite length of PC12-E2 cells grown on NCAM-140-transfected and vector-transfected fibroblasts to 100%. Statistical evaluations were performed using a two-sided Student's *t*-test.

Dynamic light scattering (DLS) measurements

Measurements were performed using a DynaPro-MS/X instrument (Protein Solutions) at 18°C. The deglycosylated preparations of Ig1-2-3 (4 mg ml^{-1}), Ig1-2-3mut (4 mg ml^{-1}) and Ig3 (10 mg ml^{-1}) in PBS pH 7.4 were used to determine the molecular weight of the recombinant proteins in solution.

Results and Discussion

The X-ray structure of the Ig1-2-3 modules of NCAM

The X-ray structure of NCAM Ig1-2-3 was determined to 2.0 Å resolution (Table 1). In the structure of Ig1-2-3, the Ig1 and Ig2 modules are positioned in an extended conformation with Ig3 oriented at an angle of approximately 45° to the Ig1-Ig2 axis (Figure 1). The linker regions between Ig1-Ig2 and between Ig2-Ig3 are short and comprise only two (Lys98 – Leu99) and one (Asn190) residues, respectively. The overall structure of the Ig1 and Ig2 modules is very similar to the previously determined Ig1-2 structure (Kasper et al., 2000) with root mean square deviations (r.m.s.d.) of 0.7 (96 C□ atoms) and 0.8 Å (93 C□ atoms), respectively. In the Ig1-2-3 structure, the tilt angle between Ig1 and Ig2 is 11° and thereby differs by 13° compared to the Ig1-2 structure.

The 98-residue Ig3 module of rat NCAM adopts the topology of an intermediate type 1 (I1) set Ig module (Casasnovas et al., 1998). In the Ig3 module, the classical β-sandwich consists of two β-sheets with a total of nine β-strands (Figure 1B). The A, B, D, and E β-strands make up one sheet and the A', C, C', F, and G β-strands the second sheet. A cysteine bridge Cys216 – Cys269 connects the two β-sheets. All strands are anti-parallel except for the A' strand, which runs parallel to the C-terminal part of the G strand. Ig3 contains one site for N-linked glycosylation at Asn203 positioned in the A' strand. The E-F loop (residues Lys261 – Asp263) forms a 3_{10} α-helical turn. The overall structure of rat Ig3 is similar to the structure of chicken Ig3 (Atkins et al., 2001) with r.m.s.d. of 1.65 Å (95 Cα atoms).

Parallel interactions between Ig modules

Several characteristic interactions are observed in the structure of the NCAM Ig1-2-3 fragment which may be divided into two groups: Interactions where the long axes (N- to C-terminus) of two interacting Ig1-2-3 molecules are oriented in a parallel manner and interactions where the long axes are oriented in an anti-parallel manner. One parallel interaction and three major anti-parallel interactions are observed in the crystal.

The parallel, cross-like dimer interaction of NCAM Ig1-2-3 involves the Ig1 and Ig2 modules (Figure 2). The total buried surface area of this interface is 1594 $Å^2$ (per dimer), which is similar to that previously observed in the Ig1-2 cross-like dimers (Kasper et al., 2000). The most prominent feature of the Ig1-to-Ig2 interaction is the intercalation of two aromatic residues of Ig1, Phe19 and Tyr65, into hydrophobic pockets formed by Ig2 residues (Figure 3A), which was also observed in the Ig1-2 structure. However, a tighter Ig1 to Ig2 binding interface is observed in the Ig1-2-3 structure, where the hydroxyl group of Tyr65 forms a direct hydrogen bond (H-bond) with Glu171, instead of a water-mediated H-bond as observed in Ig1-2. Tyr65 also makes three H-bonds to the side chains of Lys133, Glu171, and Arg173. Arg173 forms part of the Ig2 hydrophobic pocket and makes two H-bonds to Thr63. The parallel orientation of the Arg173 and Phe19 side chains and the distance between the Nε atom of the guanidinium group of Arg173 and the Cζ atom of the benzene ring of Phe19 (3.4 Å) suggest a cation-π interaction between these two residues (Flocco and Mowbray, 1994).

Dynamic Light Scattering (DLS) measurements showed that deglycosylated Ig1-2-3 forms a single species of molecules in solution with a molecular weight of ~78 kDa,

corresponding to a dimer. In order to demonstrate that Ig1-2-3 dimerization is mediated by the observed Ig1 to Ig2 binding, we produced a mutant of Ig1-2-3 (Ig1-2-3mut) containing three Ala substitutions: E11A, E16A, and K18A. These mutations have previously been shown to completely abolish dimerization of the Ig1-2 NCAM fragment in solution (Jensen et al., 1999). In the present structure Glu11 and Glu16 form intramolecular salt bridges, respectively, with Arg177 and Lys98 from the Ig1 to Ig2 linker region (not shown). These salt bridges probably contribute to the proper orientation of Ig1 with respect to Ig2 and therefore are important for the Ig1-to-Ig2 interaction. Lys18 forms an H-bond with the carboxyl group of Arg177 from the Ig2 module stabilizing the Ig1-Ig2 interaction (Figure 3A). Lys18 is located near Phe19, which is the critical residue for the Ig1-to-Ig2 interaction as it was clearly demonstrated earlier (Atkins et al., 2001). Therefore, disruption of the Lys18 - Arg177 H-bond may affect the orientation of Phe19 leading to elimination of the Ig1-to-Ig2 interaction. The molecular weight of the Ig1-2-3mut fragment was determined by DLS to be ~34 kDa, indicating a monomer. This confirms that Ig1-2-3 dimerization is mediated by Ig1-to-Ig2 binding.

Parallel (*cis*) interactions are not uncommon among cell adhesion molecules. Thus, *cis* dimerization has been demonstrated for the cell adhesion molecules C-CAM1, C-CAM2, ICAM-1, nectin-2α, and JAM belonging to the Ig superfamily (Hunter et al., 1996; Casasnovas et al., 1998; Miyahara et al., 2000; Kostrewa et al., 2001) as well as for N-, E-, and C- cadherins (Shapiro et al., 1995; Takeda et al., 1999; Brieher et al., 1996). It was shown that the dimeric form of C-cadherin is capable of adhesion, whereas the monomeric form is not (Brieher et al., 1996).

Anti-parallel interactions between Ig modules

An anti-parallel interaction takes place between the Ig2 and Ig3 modules of two Ig1-2-3 molecules, thereby forming arrays of Ig1-2-3 dimers (Figure 2A,B). Ig2 of one molecule binds to Ig3 of a second molecule, and *vice versa* (Figure 3B). The residues involved are 112-115, 143-146, and 158-161 from the B-strand, CD-loop/D-strand, and E-strand of Ig2, and residues 200-205, 261, and 278-289 from the A'-strand, EF-loop, and G-strand of Ig3. A central element of this interaction is the intercalation of the side chain of Phe287 from Ig3 into a hydrophobic pocket formed by the side chains of Val145, Arg146, and Arg158 of the Ig2 module and Lys285 from Ig3. Arg158 is also involved in water-mediated hydrogen bonding to residues Lys261 and Ala288, and Gly159 makes a direct H-bond to Asn203.

The crystal packing leaves room for glycosylation at Asn203. In order to accommodate N-linked glycosylation at this site, the side chain of Asn203 has to adopt another rotamer conformation. Thereby, the carbohydrate will point away from the binding site and towards a solvent channel in the crystal, and consequently Asn203 will not interfere with Ig2-Ig3 interactions. An interaction between the two Ig3 modules is observed at the interface, as Gln196 makes a water-mediated H-bond with Gln278. The total buried surface of the Ig2-to-Ig3 interface is 1407 Å^2 per dimer. According to Janin (1997), the probability of finding a non-specific interface of the size of the Ig2-to-Ig3 contact is only 1.9%.

Another anti-parallel interaction between two Ig1-2-3 molecules is formed between two Ig2 modules (Figure 2C,D). This interaction involves residues 103-121 and 150-158 of the AA'-loop/A'-strand/A'B-loop and the DE-loop/E-strand and has the total buried surface of 958 Å^2 per dimer (Figure 3C). Here, the central residue appears to be Glu114, which makes two H-bonds to Ser151 (side chain and backbone). Apart from an extensive hydrogen-bonding network, especially through water molecules, Val117, Val119, Leu150, and Tyr154 of both Ig2 modules form a number of hydrophobic contacts with each other at the Ig2-to-Ig2 interface (not shown).

A slightly smaller anti-parallel interaction (858 Å^2 of total buried surface per dimer) is formed between the Ig1 and Ig3 modules (Figure 2C,D), involving residues 32-47 and 76-88 from the C-strand/CC'-loop/C'-strand/C'D-loop and F-strand/FG-loop/G-strand in Ig1, and residues 198, 213-223, and 248-253 from the A-strand, B-strand/BC-loop, and D-strand/DE-loop in Ig3 (Figure 3D). Arg198 and Asp249 form direct H-bonds to the backbone oxygen atoms of Ala81 and Glu82 and two salt bridges with Lys76, respectively. Additionally, one water-mediated H-bond is formed between Lys42 and Asp250, one between Ser44 and Gly220, and two between Ser44 and Glu223. The conserved Phe36 and Phe221 are packed against Asp249 and Gln47, respectively. Together two Ig1-to-Ig3 interaction sites and one Ig2-to-Ig2 site make up a predominant contact between Ig1-2-3 dimers in the crystal (2654 Å^2) forming the second array of Ig1-2-3 dimers (Figure 2C,D) perpendicular to the Ig2-to-Ig3-mediated array (Figure 2A,B). Contact areas of similar sizes have been found in other CAMs. *Cis* dimers of human ICAM-1 and mouse JAM have 1100 Å^2 and 1200 Å^2 of total buried surface area (per dimer), respectively (Casasnovas et al. 1998; Kostrewa et al., 2001), whereas *trans* dimers of rat CD2 and chicken axonin-1/TAG-1 have even larger contact areas of 1300 Å^2 and 2000 Å^2 (Jones et al., 1992; Freigang et al., 2000).

The Ig3 module does not dimerize in solution

The molecular weight of the deglycosylated Ig3 module in solution was determined by DLS to be ~11.2 kDa, which corresponds to a monomer. In agreement with this observation, a small anti-parallel contact is formed between two Ig3 modules in the crystal, involving the polar residues 260-264 from the EF-loop with a total buried area of only 487 Å^2 per dimer (not shown). The Ig3-to-Ig3 contact does not involve residues of the previously suggested homophilic binding sequence (Rao et al., 1992), and probably only reflects a crystal packing contact.

Ig3 inhibits NCAM-dependent neurite outgrowth

NCAM-NCAM interaction is known to induce neurite outgrowth from NCAM-expressing PC12-E2 cells grown on a confluent monolayer of NCAM-expressing fibroblasts (Kolkova et al., 2000). Inhibition of the NCAM-NCAM interaction will therefore inhibit neurite outgrowth in PC12-E2 cells.

In order to examine the biological significance of the observed Ig1-to-Ig3 and Ig2-to-Ig3 contacts in the structure of NCAM Ig1-2-3, we tested the inhibitory effect of the recombinant Ig3 module on NCAM-NCAM adhesion. Furthermore, we prepared two Ig3 mutants containing mutations of the residues R198A, D249G, E253A (Ig3mut1) of the Ig1-to-Ig3 contact site (see Figure 3D) and K285A, F287A (Ig3mut2) of the Ig2-to-Ig3 contact site (see Figure 3B). In Figure 4 it can be seen that the wildtype Ig3 module (Ig3wt) indeed has an inhibitory effect, whereas both mutants are inactive, thereby strongly supporting that both the Ig1-to-Ig3 and Ig2-to-Ig3 contact sites are participating in homophilic interactions.

A similar co-culture test-system of NCAM-expressing chicken retinal ganglion cells grown on top of NCAM-140-transfected mouse L-cells has been successfully used to demonstrate a disruptive effect of mutations in the Ig3 module homophilic binding site (Ig1-to-Ig3 binding site in the present work) as well as to show an inhibition of neurite outgrowth by synthetic peptides representing this homophilic binding site (Sandig et al. 1994).

Interaction interface peptides inhibit neurite outgrowth

It has previously been demonstrated that peptides representing homophilic binding sequences from Ig3 and Ig2 modules of NCAM inhibit NCAM-mediated cell aggregation (Rao et al., 1992; Sandig et al. 1994; Rao et al., 1994; Soroka et al.

2002). Therefore, in order to further examine the biological significance of the observed Ig1-to-Ig2, Ig1-to-Ig3, and Ig2-to-Ig3 contacts in the structure of NCAM Ig1-2-3, we tested the inhibitory effect of a series of peptides representing amino-acid sequences from the observed contact areas (Figure 4).

The Ig1-to-Ig2 contact was represented by a peptide 10-GEISVGESKFFL-21 (P1-B) (SEQ ID NO: 19), covering the B D-strand of Ig1 and containing the key residue Phe19 in the Ig1-to-Ig2 binding (Kasper et al., 2000; Atkins et al., 2001). As a negative control, two peptides GEISVGESKAFL (P1-B-F19A) (SEQ ID NO:21) and GEISVGESKAAL (P1-B-F19A-F20A) (SEQ ID NO: 22) containing a single Ala substitution of F19 and a double Ala substitution of both F19 and F20, respectively, were used.

The Ig1-to-Ig3 contact was represented by a peptide 244-KHIFSDDSSELTIRNVDKNDE-264 (P3-DE) (SEQ ID NO: 20), covering the sequence of the D and E β-strands and the E-F loop of the Ig3 module. This peptide is homologous to the sequence previously suggested to be a homophilic binding site in the Ig3 module of chicken NCAM (243-KYSFNYDGSELIIKKVDKSDE-263) (SEQ ID NO: 23) (Rao et al., 1992). As a negative control, a truncated version of the P3-DE peptide 244-KHIFSDDSSE-253 (P3-DE-trunc) (SEQ ID NO: 24) was used. The P3-DE-trunc peptide is homologous to the 243-KYSFNYDGSE-252 (SEQ ID NO: 25) chicken sequence which was less potent than the longer sequence (Rao et al., 1992).

The Ig2-to-Ig3 contact was represented by a peptide 281-SIHLKVFAK-289 (P3-G) (SEQ ID NO: 13) from the Ig3 module. This sequence covers the C-terminal part of the G β-strand including the solvent-exposed Phe287. As negative controls, two peptides SIHLAVAAK (P3-G-K285A-F287S) (SEQ ID NO: 26) and SIHLAVGAK (P3-G-K285A-F287G) (SEQ ID NO: 27) with substitutions of K285 and F287 were used. Both P1-B and P3-G peptides contain two hydrophobic residues (Ile and Val/Leu) close to their N-termini and at least one Phe residue close to their C-termini. As a control peptide with similar hydrophobic properties we selected a peptide 213-TLVADADGFPEP-224 (P3-B) (SEQ ID NO: 3) covering the B β-strand and B-C loop of the Ig3 module, and including Gly220, Phe221, and Glu223 involved in Ig1-to-Ig3 binding. In spite of sequence similarity with P1-B and P3-G peptides, the P3-B peptide was not active (Figure 4G). This is probably due to the fact that Phe221 in Ig3 is partially solvent exposed and Gly220 and Glu223 form water-mediated hydrogen bonds (Figure 3D). In contrast, the peptides P1-B, P3-DE, and P3-G either

contain Phe buried in a hydrophobic pocket or residues forming direct H-bonds (Figure 3).

In conclusion, the cell co-culture experiments demonstrated that the P1-B, P3-DE, and P3-G peptides all inhibited NCAM-stimulated neurite outgrowth, indicating an impaired NCAM-NCAM binding between the two cell layers. The corresponding control peptides had little or no inhibitory effect (Figure 4G). The P1-B peptide interferes with the Ig1-to-Ig2 interaction and thereby inhibits the Ig1-Ig2-mediated *cis* dimerization of NCAM. In the crystals of the Ig1-2-3 module zipper-like arrays of NCAM *cis* dimers are observed, reflecting *trans* interactions of NCAM. *Trans* interactions therefore seem to require *cis* dimerization of NCAM molecules (Figure 2). The P3-DE and P3-G peptides will not affect *cis* interactions but interfere with *trans* interactions. Since the NCAM-dependent neurite outgrowth relies on NCAM-NCAM interactions between the two cell layers, an inhibition of these interactions will directly affect NCAM-mediated neurite outgrowth.

In our study, we show that mutations in the peptides derived from the Ig3 module produce the same effect as that of the similar mutations in the Ig3 module. This demonstrates that in this experimental setup the employed peptides mimic the Ig3 module, and thus can be used as a convenient and simple tool for further analysis. Moreover, the peptides representing the sequence of the Ig3 module homophilic binding site of chicken NCAM (Ig1-to-Ig3 binding site in the present work) have been previously used to identify and characterize the Ig3 module homophilic binding site (Rao et al., 1992; Sandig et al., 1994; Rao et al., 1994). These results, combined with the Ig3 mutation studies, provide strong evidence for a biological role of the observed Ig1-to-Ig2, Ig1-to-Ig3, and Ig2-to-Ig3 contacts.

Novel zipper mechanism for NCAM homophilic adhesion

The crystal structure of the Ig1-2-3 fragment reveals novel interactions between the Ig1 and Ig3 and the Ig2 and Ig3 modules of NCAM, as well as shows previously observed Ig1-to-Ig2 and Ig2-to-Ig2 interactions (Kasper et al., 2000). Together, these contacts mediate formation of two perpendicular zipper-like arrays of the Ig1-2-3 dimers (Figure 2). The parallel interaction of the NCAM Ig1-2-3 molecules in the crystal mediated by the Ig1-to-Ig2 contact may reflect an interaction between NCAM molecules present on the same cell surface – *cis* interaction. The anti-parallel interactions mediated by the Ig1-to-Ig3, Ig2-to-Ig2, and the Ig2-to-Ig3 contacts may reflect the interaction of NCAM molecules present on opposing cells - *trans*

interactions. Based on all presented observations, we propose a model for NCAM homophilic adhesion, consisting of two zipper-like arrays of NCAM molecules (Figure 5). In the "compact" zipper (Figure 5A), NCAM *cis* dimers originating from opposing cell membranes are arranged as arrays through Ig1-to-Ig3 and Ig2-to-Ig2 interactions. We speculate that "compact" zippers are likely to form first as they allow larger distances between opposing cell membranes than the perpendicular "flat" zippers. In the "flat" zipper (Figure 5B), the Ig2-to-Ig3 interactions suggest a lateral association between the NCAM "compact" zippers thereby forming a double zipper adhesion complex (Figure 5C). The glycosylation at Asn203 of Ig3 (Figure 2) is not likely to interfere with the ability to form the zippers as supported by the fact that the glycosylated Ig3 module inhibits NCAM-mediated neurite outgrowth, whereas glycosylated Ig3mut2 containing mutations at the Ig2-Ig3 binding site is inactive (Figure 4F,G). In the "compact" zipper, the heparin binding sites (133-KHKGRDVILKKDVRFI-148) (SEQ ID NO: 39) (Cole and Akeson, 1989) of Ig1-2-3 molecules are solvent exposed (Figure 2C,D) and therefore accessible for binding to heparin and heparan sulfate molecules, suggesting that NCAM can be engaged in homophilic and heterophilic interactions simultaneously.

In order to accommodate all seven extracellular modules of NCAM within a typical distance between plasma membranes of ~30 nm (Hall and Rutishauser, 1987), a bend has to be introduced in the NCAM molecules in our model (Figure 5). Analyses of NCAM by electron microscopy have revealed such a bent rod-like structure (Hall and Rutishauser, 1987; Becker et al., 1989). The angle of the bend at the hinge-region between N-terminal (~18 nm) and C-terminal (~10 nm) parts varies considerably (50-140°) with an average value of 98° (Becker et al., 1989) and presumably provides sufficient internal flexibility for NCAM to fit within the cell-cell distance. Based on these studies and on an average length of ~4.3 nm for an Ig module (present work) and ~3.5 nm for a FnIII module (Leahy et al., 1996), the hinge region is most likely located after Ig4. A multiple sequence alignment of NCAM sequences from various species of vertebrates reveals conserved Pro, Lys, and Gly residues in the PKLQGP sequence connecting the Ig4 and Ig5 modules. Since Pro and Gly are typically associated with polypeptide bends, this sequence is likely to introduce a bend between Ig4 and Ig5 modules. The double zipper observed in the crystal (Figure 5C) presents Ig modules 1 to 3 at differing heights, implying that the NCAM molecules upon co-existence of the zippers are bent with

different angles. This is in accordance with the electron microscopy data (Hall and Rutishauser, 1987; Becker et al., 1989).

Although *cis* interactions between the Ig1-Ig2 modules do not mediate cell-cell interactions themselves, they probably contribute to the stability of the *trans* interactions. This contention is supported by the cell co-culture experiments using the P1-B peptide corresponding to the site in Ig1 binding to Ig2 (Figure 4). Furthermore, an inhibitory effect on cell aggregation was recently demonstrated for a peptide 172-GRILARGEINFK-182 (P2 peptide) (SEQ ID NO: 28) representing the site in the Ig2 module binding to the Ig1 module (Soroka et al., 2002). Therefore, we suggest that the formation of *cis* dimers may be a prerequisite for the establishment of *trans* interactions.

To our knowledge, only three X-ray structures of Ig module containing adhesion molecules have been determined comprising three or more Ig modules (axonin-1/TAG1 (Freigang et al., 2000), hemolin (Su et al., 1998), and CD4 (Wu et al., 1997). A similar zipper-like array of *trans*-interacting *cis* homodimers has been observed in the crystal structure of the junctional adhesion molecule (JAM) (Kostrewa et al., 2001). A zipper-like mechanism of homophilic interactions was also suggested for axonin-1/TAG-1 (Freigang et al., 2000), where molecules alternately provided by opposed membranes form a linear zipper-like array. However, the double zipper formed by NCAM differs fundamentally from the previously described zippers.

In conclusion, we here present a novel model for NCAM homophilic binding, which is based on the formation of zippers. The model is in agreement with a number of studies demonstrating that the Ig1, Ig2, and Ig3 modules all are involved in NCAM homophilic binding (Rao et al., 1992; Sandig et al., 1994; Kiselyov et al., 1997; Jensen et al., 1999; Kasper et al., 2000; Atkins et al., 2001) and reconciles a large body of conflicting biological data. The crystal structure of the Ig1-2-3 fragment reveals details of two so far unknown interactions between Ig1 and Ig3 and between Ig2 and Ig3. Interestingly, the Ig1 and Ig2 modules of NCAM mediate both *cis* and *trans* interactions simultaneously, whereas Ig3 is involved only in *trans* interactions. All taken together, our study implies that it is the joined forces of the first three Ig modules that confer the strength of the NCAM-mediated adhesion.

Claims

1. A method of modulating cell differentiation and/or survival of the neural cell adhesion molecule (NCAM) presenting cells comprising

a) providing a candidate compound capable of

i) interacting with the Ig1 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) interacting with the Ig2 module of NCAM, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iv) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

v) interacting with the Ig2 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules,

b) providing at least one NCAM presenting cell;

c) contacting the at least one NCAM presenting cell with at least one candidate compound of (a), and thereby modulating cell differentiation and/or survival of the at least one NCAM presenting cell.

2. The method of claim 1, wherein the cell differentiation and/or survival are mediated by NCAM.

3. The method of the claims 1-2, wherein the NCAM is mammalian NCAM, or variants, or fragments thereof.

4. The method of claim 1, wherein the candidate compound is selected from the group comprising peptides, carbohydrates, lipids, or co-polymers of amino acids with other organic molecules.

5. The method of claim 4, wherein the candidate compound is selected from the group comprising peptide fragments or variants of peptide fragments derived from the sequence of NCAM having the NCBI accession numbers NP_113709 (SEQ ID NO: 40).

6. A method for screening of a candidate compound for capability of modulating cell differentiation and/or survival of NCAM presenting cells, said compound is capable of,

i) interacting with the Ig1 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) interacting with the Ig2 module of NCAM, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iv) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

v) interacting with the Ig2 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules,

said method comprising

a) providing the candidate compound;

b) providing a compound comprising the NCAM Ig1-2-3 module, or fragments of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules;

c) detecting interaction between compounds of (a) and (b).

7. The screening method of claim 6, wherein the candidate compound is selected from the group comprising peptides, carbohydrates, lipids, or co-polymers of amino acids with other organic molecules.

8. The screening method of claim 6, wherein the compound of step (b) is a solution of the NCAM Ig1-2-3 module, or fragments of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules.

9. The screening method of claim 8, wherein the solution is an aquatic solution

10. The screening method of claim 6, wherein the compound of step (b) is a crystalline protein comprising of the Ig1-2-3 module of NCAM.

11. A crystal of a polypeptide comprising the Ig1-2-3 module of NCAM comprising at least 289 consecutive amino acids from the sequence of rat NCAM (NCBI accession number NP_113709) (SEQ ID NO: 40), said module comprising a homophylic binding site of NCAM.

12. The crystal according to claim 11, wherein the polypeptide comprises aa 1 to 289 of SEQ ID NO: 40.

13. The crystal according to claim 11, wherein the polypeptide consists of aa 1 to 289 of SEQ ID NO: 40 and an extra amino acid sequence of 1 to 4 amino acids residues.

14. The crystal according to claim 11, wherein the crystal comprises the polypeptide according to claims 11, 12 or 13 and a candidate compound, said candidate compound is a candidate compound according to claim 1 or 6.

15. The crystal according to claim 11, wherein said crystal diffracts X-rays for determination of atomic co-ordinates to a resolution of at least 4 Å.

16. The crystal according to claim 11, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates to a resolution at most 5. 0 Å.

17. The crystal according to claims 15 or 16, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates to a resolution 1. 5 Å.

18. The crystal according to claim 11, wherein said crystal comprises atoms arranged in a spatial relationship represented by the structure co-ordinates of Table 2 or by coordinates having a root mean square deviation therefrom of not more than 2.5 Å.

19. The crystal according to claim 11, wherein said crystal has unit cell dimensions of a=51.5 Å, b=108.5 Å, c=149.0 Å, alpha=90°, beta=90°, gamma=90°.

20. A method of preparing a crystal of a polypeptide comprising the Ig1-2-3 module of NCAM comprising at least 289 consecutive amino acids from the sequence of rat NCAM (NCBI accession number NP_113709) (SEQ ID NO: 40), said module comprising a homophylic binding site of NCAM, wherein said method comprises the steps of

i) providing said polypeptide;
ii) optionally providing a compound capable of interacting with said polypeptide;
iii) growing the crystal under conditions wherein said polypeptide, and optionally said compound, is incubated in a buffer comprising in the range of 5 to 25% polyethylene glycol, in the range of 0.01 M to 0.5M salt, in the range of 1 to 10% of an alcohol selected from the group consisting of glycerol and 2-methyl-2,4-penthanediol, wherein said buffer has a pH in the range of 6 to 9;
iv) thereby preparing said crystal.

21. An assay for selecting a candidate compound capable of modulating cell differentiation and/or survival of NCAM presenting cells, comprising the steps of

i) incubating at least one candidate compound and a compound comprising the Ig1-2-3 module of NCAM in a solution followed by
ii) preparing a crystal according to the method of claim 20, said crystal comprising the at least one candidate compound and the Ig1-2-3 module of NCAM;
iii) determining the three-dimensional structure of the crystal of step (ii) followed by

iv) the selection of the candidate compound capable of (1) interacting with the Ig1 module and thereby modulating the interaction between the Ig3 and Ig1 module in the crystal of the Ig1-2-3 module of NCAM, and/or (2) interacting to the Ig3 module and thereby modulating the interaction between the Ig1 and the Ig3 module in the crystal of the Ig1-2-3 module of NCAM, and/or (3) interacting with the Ig2 module and thereby modulating the interaction between the Ig3 and Ig2 module in the crystal of the Ig1-2-3 module of NCAM and/or (4) interacting with the Ig3 module and thereby modulating the interaction between the Ig2 and Ig3 module in the crystal of the Ig1-2-3 module of NCAM, and/or (5) interacting with the Ig2 module and thereby modulating the interaction of the Ig2 and Ig2 module in the crystal of the Ig1-2-3 module of NCAM;

v) contacting the candidate compound of step (iv) with an NCAM presenting cell in vitro followed by

vi) evaluating the cellular response to the candidate compound.

22. The assay of claim 21, wherein steps (i) and (ii) are substituted by the step of incubating the crystal of the Ig1-2-3 module of NCAM as defined in claims 11-19 with a candidate compound in solution, and the steps (iii-iv) are as in claim 18.

23. A screening method for selecting a candidate compound capable of modulating cell differentiation and/or survival of NCAM presenting cells, comprising the steps of

i) providing a polypeptide comprising the Ig1-2-3 module of NCAM, or parts of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules

ii) generating a structural model of the Ig1-2-3 module of NCAM, or parts of said module, such as Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules, by computer modelling techniques;

iii) designing a candidate compound into the structure of said generated model;

iv) testing the candidate compound of step (iii) in an in vitro or in vivo assay.

24. The screening method of claim 23, wherein the computer generated model is the structural model of the Ig1-2-3 module of NCAM, or parts of said module, such as the Ig1, Ig2, Ig3, or Ig1-2, or Ig2-3 modules in solution.

25. The screening method of claim 13, wherein the computer generated model is the structural model of a crystal of the Ig1-2-3 module of NCAM according to claims 11-15, or parts of said module such as Ig1, Ig2, Ig3, Ig1-2 or Ig2-3 modules.

26. The method of claim 1, 6 or 23, wherein the candidate is for the manufacture of a medicament for the treatment of normal, degenerated or damaged NCAM presenting cells.

27. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for the treatment comprising the stimulation of differentiation of N-CAM presenting cells and/or survival thereof.

28. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament comprising treatment of diseases and conditions of the central and peripheral nervous system, or of the muscles or of various organs.

29. The method of claim 1, 6 23, wherein the candidate compound is for the manufacture of a medicament for the treatment of diseases or conditions of the central and peripheral nervous system, such as postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel.

30. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for the treatment of postoperative nerve damage.

traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression.

31. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for the promotion of wound-healing.

32. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for the treatment of cancer.

33. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for the prevention of cell death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis.

34. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for revascularsation.

35. The method of claim 1, 6 or 23, wherein the candidate compound is for the manufacture of a medicament for the stimulation of the ability to learn and/or of the short and/or long-term memory.

36. Use of a crystal of the Ig1-2-3 module of NCAM, of a part of said module such as the Ig1, Ig2, Ig3, Ig1-2, Ig2-3 and Ig1-3 modules, for the manufacture of a kit for screening a candidate compound capable of modulating NCAM homophylic adhesion-dependent cell differentiation and/or survival.

37. A kit for screening a candidate compound capable of modulating NCAM homophylic adhesion dependent cell differentiation and/or survival, said kit, comprising

i) the Ig1-2-3 module of NCAM in solution, and/or

ii) a crystal of the Ig1-2-3 module of NCAM as defined in claims 11-15.

38. A candidate compound capable of

i) interacting with the Ig1 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig1 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

ii) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig1 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iii) interacting with the Ig2 module of NCAM, and thereby mimicking the interaction between Ig2 and Ig3 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

iv) interacting with the Ig3 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig3 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules, and/or

v) interacting with the Ig2 module of NCAM, and thereby mimicking and/or modulating the interaction between the Ig2 and Ig2 modules of NCAM, wherein said modules are from two individual NCAM molecules,

said compound is selected from the group comprising peptide fragments having the amino acid sequences selected from the group

WFSPNGEKLSPNQ (SEQ ID NO: 1)
YKCVVTAEDGTQSE (SEQ ID NO: 2)
TLVADADGFPEP (SEQ ID NO: 3)
QIRGIKKTD (SEQ ID NO: 4)
DVR (SEQ ID NO: 5)
RGIKKTD (SEQ ID NO: 6)
DVRRGIKKTD (SEQ ID NO: 7)
KEGED (SEQ ID NO: 8)
IRGIKKTD (SEQ ID NO: 9)
KEGEDGIRGIKKTD (SEQ ID NO: 10)
DKNDE (SEQ ID NO: 11)
TVQARNSIVNAT (SEQ ID NO: 12)
SIHLKVFAK (SEQ ID NO: 13)
LSNNYLQIR (SEQ ID NO: 14)
RFIVLSNNYLQI (SEQ ID NO: 15)
KKDVRFIVLSNNYLQI (SEQ ID NO: 16)
QEFKEGEDAVIV (SEQ ID NO: 17)

KEGEDAVIVCD (SEQ ID NO: 18)
GEISVGESKFFL (SEQ ID NO: 19)
KHIFSDDSSELTIRNVDKNDE (SEQ ID NO: 20),
or fragments, or variants or combinations thereof, wherein said amino acid sequences being indentified by the screening method according to claim 23.

39. The compound according to claim 38, said compound having the amino acid sequence WFSPNGEKLSPNQ set forth in SEQ ID NO: 1, fragments or variants thereof.

40. The compound according to claim 38, said compound having the amino acid sequence YKCVVTAEDGTQSE set forth in SEQ ID NO: 2, fragments or variants thereof.

41. The compound according to claim 38, said compound having the amino acid sequence TLVADADGFPEP set forth in SEQ ID NO: 3, fragments or variants thereof.

42. The compound according to claim 38, said compound having the amino acid sequence QIRGIKKTD set forth in SEQ ID NO: 4, fragments or variants thereof.

43. The compound according to claim 38, said compound having the amino acid sequence DVR set forth in SEQ ID NO: 5, fragments or variants thereof.

44. The compound according to claim 38, said compound having the amino acid sequence RGIKKTD set forth in SEQ ID NO: 6, fragments or variants thereof.

45. The compound according to claim 38, said compound having the amino acid sequence DVRRGIKKTD set forth in SEQ ID NO: 7, fragments or variants thereof.

46. The compound according to claim 38, said compound having the amino acid sequence KEGED set forth in SEQ ID NO: 8, fragments or variants thereof.

47. The compound according to claim 38, said compound having the amino acid sequence IRGIKKTD set forth in SEQ ID NO: 9, fragments or variants thereof.

48. The compound according to claim 38, said compound having the amino acid sequence KEGEDGIRGIKKTD set forth in SEQ ID NO: 10, fragments or variants thereof.

49. The compound according to claim 38, said compound having the amino acid sequence DKNDE set forth in SEQ ID NO: 11, fragments or variants thereof.

50. The compound according to claim 38, said compound having the amino acid sequence TVQARNSIVNAT set forth in SEQ ID NO: 12, fragments or variants thereof.

51. The compound according to claim 38, said compound having the amino acid sequence SIHLKVFAK set forth in SEQ ID NO: 13, fragments or variants thereof.

52. The compound according to claim 38, said compound having the amino acid sequence LSNNYLQIR set forth in SEQ ID NO: 14, fragments or variants thereof.

53. The compound according to claim 38, said compound having the amino acid sequence RFIVLSNNYLQI set forth in SEQ ID NO: 15, fragments or variants thereof.

54. The compound according to claim 38, said compound having the amino acid sequence KKDVRFIVLSNNYLQI set forth in SEQ ID NO: 16, fragments or variants thereof.

55. The compound according to claim 38, said compound having the amino acid sequence QEFKEGEDAVIV set forth in SEQ ID NO: 17, fragments or variants thereof.

56. The compound according to claim 38, said compound having the amino acid sequence KEGEDAVIVCD set forth in SEQ ID NO: 18, fragments or variants thereof.

57. Use of one or more compounds as defined in any of the claims 38-56 for the manufacture a medicament for the treatment of conditions as defined in any of the claims 26-35.

Table 1. Crystallographic data and refinement statistics

	Native data set
Wavelength (Å)	1.0526
Resolution range (Å)[1]	50.0-2.0 (2.07-2.0)
No. of observed reflections	164,206
No. of unique reflections	27,881
No. of reflections in R_{free} set	828
Completeness (%)	99.2(99.4)
I/σ(I)	19.6(1.4)
(R_{merge}) (%)[2]	3.9(20.9)
R_{cryst}/R_{free} (%)[3]	21.8/23.8
No. of refined non-hydrogen atoms[4]	
protein	2248
water	265
Average B-factor (all atoms, Å^2)	60
Wilson B-factor (Å^2)	45
R.m.s. Δ bond lengths/angles[5]	0.0081/1.7
Residues in allowed regions (%)[6]	97%

[1]Values in parentheses are statistics for the highest resolution bin.
[2]$R_{merge}\ (I) = \sum_{hkl} |Ihkl - \langle Ihkl \rangle| / \sum_{hkl} Ihkl$, where $Ihkl$ is the measured intensity of the reflections with indices *hkl*.
[3]$R = \sum_{hkl} ||Fo| - |Fc|| / \sum |Fo|$, where $|Fo|$ and $|Fc|$ are the observed and calculated structure factor amplitudes for reflection hkl, applied to the work (R_{cryst}=97%) and test (R_{free}=3%) sets, respectively.
[4]Residues -2, 239 and 240 were not located. Residues originating from the cloning site were given negative integers.
[5]Root mean squared deviations (rms Δ) in bond length and angles from ideal values.
[6]The Ramachandran plot was calculated according to Kleywegt and Jones, (1996).

Table 2

```
HEADER    CELL ADHESION                                  15-SEP-03   1QZ1
TITLE     CRYSTAL STRUCTURE OF THE IG 1-2-3 FRAGMENT OF NCAM
COMPND    MOL_ID: 1;
COMPND   2 MOLECULE: NEURAL CELL ADHESION MOLECULE 1, 140 KDA ISOFORM;
COMPND   3 CHAIN: A;
COMPND   4 FRAGMENT: IG MODULES 1-2-3;
COMPND   5 SYNONYM: N-CAM 140, NCAM-140;
COMPND   6 ENGINEERED: YES
SOURCE    MOL_ID: 1;
SOURCE   2 ORGANISM_SCIENTIFIC: RATTUS NORVEGICUS;
SOURCE   3 ORGANISM_COMMON: RAT;
SOURCE   4 GENE: NCAM1;
SOURCE   5 EXPRESSION_SYSTEM: PICHIA PASTORIS;
SOURCE   6 EXPRESSION_SYSTEM_COMMON: FUNGUS;
SOURCE   7 EXPRESSION_SYSTEM_STRAIN: GS-115;
SOURCE   8 EXPRESSION_SYSTEM_VECTOR_TYPE: PLASMID;
SOURCE   9 EXPRESSION_SYSTEM_PLASMID: PHIL-S1
KEYWDS    IG MODULES, CELL ADHESION, NCAM
EXPDTA    X-RAY DIFFRACTION
AUTHOR    V.SOROKA, K.KOLKOVA, J.S.KASTRUP, K.DIEDERICHS, J.BREED,
AUTHOR   2 V.V.KISELYOV, F.M.POULSEN, I.LARSEN, W.WELTE, V.BEREZIN,
AUTHOR   3 E.BOCK, C.KASPER
JRNL        AUTH   V.SOROKA, K.KOLKOVA, J.S.KASTRUP, K.DIEDERICHS,
JRNL        AUTH 2 J.BREED, V.V. KISELYOV, F.M.POULSEN, I.LARSEN,
JRNL        AUTH 3 W.WELTE, V.BEREZIN, E.BOCK, C.KASPER
JRNL       TITL   STRUCTURE AND INTERACTIONS OF NCAM IG1-2-3 SUGGEST
JRNL       TITL 2 A NOVEL ZIPPER MECHANISM FOR HOMOPHILIC ADHESION
JRNL        REF    TO BE PUBLISHED
JRNL        REFN
REMARK    1
REMARK    1 REFERENCE 1
REMARK    1  AUTH   C.KASPER,H.RASMUSSEN,J.S.KASTRUP,S.IKEMIZU,
REMARK    1  AUTH 2 E.Y.JONES,V.BEREZIN,E.BOCK,I.K.LARSEN
REMARK    1  TITL   STRUCTURAL BASIS OF CELL-CELL ADHESION BY NCAM
REMARK    1  REF    NAT.STRUCT.BIOL.              V.   7   389 2000
REMARK    1  REFN   ASTM NSBIEW  US ISSN 1072-8368
REMARK    1 REFERENCE 2
REMARK    1  AUTH   C.KASPER,H.RASMUSSEN,V.BEREZIN,E.BOCK,I.K.LARSEN
REMARK    1  TITL   EXPRESSION, CRYSTALLIZATION AND PRELIMINARY X-RAY
REMARK    1  TITL 2 ANALYSIS OF THE TWO AMINO-TERMINAL IG DOMAINS OF
REMARK    1  TITL 3 THE NEURAL CELL ADHESION MOLECULE (NCAM).
REMARK    1  REF    ACTA CRYSTALLOGR., SECT.D     V.  55  1598 1999
REMARK    1  REFN   ASTM ABCR86  DK ISSN 0907-4449
REMARK    2
REMARK    2 RESOLUTION. 2.00 ANGSTROMS.
REMARK    3
REMARK    3 REFINEMENT.
REMARK    3   PROGRAM     : CNS 1.0
REMARK    3   AUTHORS     : BRUNGER,ADAMS,CLORE,DELANO,GROS,GROSSE-
REMARK    3                : KUNSTLEVE,JIANG,KUSZEWSKI,NILGES, PANNU,
REMARK    3                : READ,RICE,SIMONSON,WARREN
REMARK    3
REMARK    3  REFINEMENT TARGET : ENGH & HUBER
REMARK    3
REMARK    3  DATA USED IN REFINEMENT.
REMARK    3   RESOLUTION RANGE HIGH (ANGSTROMS) : 2.00
REMARK    3   RESOLUTION RANGE LOW  (ANGSTROMS) : 48.64
```

```
REMARK   3   DATA CUTOFF                (SIGMA(F)) : 0.000
REMARK   3   DATA CUTOFF HIGH              (ABS(F)) : NULL
REMARK   3   DATA CUTOFF LOW               (ABS(F)) : NULL
REMARK   3   COMPLETENESS (WORKING+TEST)     (%) : 99.2
REMARK   3   NUMBER OF REFLECTIONS                : 28289
REMARK   3
REMARK   3  FIT TO DATA USED IN REFINEMENT.
REMARK   3   CROSS-VALIDATION METHOD              : THROUGHOUT
REMARK   3   FREE R VALUE TEST SET SELECTION      : RANDOM
REMARK   3   R VALUE            (WORKING SET)    : 0.218
REMARK   3   FREE R VALUE                         : 0.238
REMARK   3   FREE R VALUE TEST SET SIZE     (%)   : NULL
REMARK   3   FREE R VALUE TEST SET COUNT          : 828
REMARK   3   ESTIMATED ERROR OF FREE R VALUE      : NULL
REMARK   3
REMARK   3  FIT IN THE HIGHEST RESOLUTION BIN.
REMARK   3   TOTAL NUMBER OF BINS USED                 : NULL
REMARK   3   BIN RESOLUTION RANGE HIGH           (A)   : 2.00
REMARK   3   BIN RESOLUTION RANGE LOW            (A)   : 2.13
REMARK   3   BIN COMPLETENESS (WORKING+TEST)     (%)   : 99.00
REMARK   3   REFLECTIONS IN BIN     (WORKING SET)      : NULL
REMARK   3   BIN R VALUE            (WORKING SET)      : 0.3730
REMARK   3   BIN FREE R VALUE                          : 0.4390
REMARK   3   BIN FREE R VALUE TEST SET SIZE     (%)   : NULL
REMARK   3   BIN FREE R VALUE TEST SET COUNT           : 148
REMARK   3   ESTIMATED ERROR OF BIN FREE R VALUE       : 0.036
REMARK   3
REMARK   3  NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK   3   PROTEIN ATOMS            : 2247
REMARK   3   NUCLEIC ACID ATOMS       : 0
REMARK   3   HETEROGEN ATOMS          : 0
REMARK   3   SOLVENT ATOMS            : 265
REMARK   3
REMARK   3  B VALUES.
REMARK   3   FROM WILSON PLOT           (A**2) : 42.00
REMARK   3   MEAN B VALUE      (OVERALL, A**2) : 60.60
REMARK   3   OVERALL ANISOTROPIC B VALUE.
REMARK   3    B11 (A**2) : 7.90000
REMARK   3    B22 (A**2) : -15.20000
REMARK   3    B33 (A**2) : 7.30000
REMARK   3    B12 (A**2) : 0.00000
REMARK   3    B13 (A**2) : 0.00000
REMARK   3    B23 (A**2) : 0.00000
REMARK   3
REMARK   3  ESTIMATED COORDINATE ERROR.
REMARK   3   ESD FROM LUZZATI PLOT          (A) : 0.30
REMARK   3   ESD FROM SIGMAA                (A) : 0.36
REMARK   3   LOW RESOLUTION CUTOFF          (A) : 5.00
REMARK   3
REMARK   3  CROSS-VALIDATED ESTIMATED COORDINATE ERROR.
REMARK   3   ESD FROM C-V LUZZATI PLOT      (A) : 0.35
REMARK   3   ESD FROM C-V SIGMAA            (A) : 0.42
REMARK   3
REMARK   3  RMS DEVIATIONS FROM IDEAL VALUES.
REMARK   3   BOND LENGTHS                   (A) : 0.008
REMARK   3   BOND ANGLES              (DEGREES) : 1.70
REMARK   3   DIHEDRAL ANGLES          (DEGREES) : 27.50
REMARK   3   IMPROPER ANGLES          (DEGREES) : 0.95
REMARK   3
```

Table 2


```
REMARK   3  ISOTROPIC THERMAL MODEL : ANISOTROPIC
REMARK   3
REMARK   3  ISOTROPIC THERMAL FACTOR RESTRAINTS.     RMS     SIGMA
REMARK   3   MAIN-CHAIN BOND              (A**2) : NULL  ; NULL
REMARK   3   MAIN-CHAIN ANGLE             (A**2) : NULL  ; NULL
REMARK   3   SIDE-CHAIN BOND              (A**2) : NULL  ; NULL
REMARK   3   SIDE-CHAIN ANGLE             (A**2) : NULL  ; NULL
REMARK   3
REMARK   3  BULK SOLVENT MODELING.
REMARK   3   METHOD USED : NULL
REMARK   3   KSOL        : NULL
REMARK   3   BSOL        : NULL
REMARK   3
REMARK   3  NCS MODEL : NULL
REMARK   3
REMARK   3  NCS RESTRAINTS.                        RMS   SIGMA/WEIGHT
REMARK   3   GROUP  1  POSITIONAL            (A) : NULL  ; NULL
REMARK   3   GROUP  1  B-FACTOR           (A**2) : NULL  ; NULL
REMARK   3
REMARK   3   PARAMETER FILE  1   : NULL
REMARK   3   TOPOLOGY FILE  1    : NULL
REMARK   3
REMARK   3  OTHER REFINEMENT REMARKS: RESIDUES 241-242 WERE NOT LOCATED IN
REMARK   3  THE ELECTRON DENSITY MAP
REMARK   4
REMARK   4 1QZ1 COMPLIES WITH FORMAT V. 2.3, 09-JULY-1998
REMARK 100
REMARK 100 THIS ENTRY HAS BEEN PROCESSED BY RCSB ON 17-SEP-2003.
REMARK 100 THE RCSB ID CODE IS RCSB020242.
REMARK 200
REMARK 200 EXPERIMENTAL DETAILS
REMARK 200  EXPERIMENT TYPE                : X-RAY DIFFRACTION
REMARK 200  DATE OF DATA COLLECTION        : 06-NOV-2000; 04-DEC-2000
REMARK 200  TEMPERATURE           (KELVIN) : 100.0
REMARK 200  PH                             : 5.20
REMARK 200  NUMBER OF CRYSTALS USED        : 1
REMARK 200
REMARK 200  SYNCHROTRON              (Y/N) : Y; N
REMARK 200  RADIATION SOURCE               : MAX II ; ROTATING ANODE
REMARK 200  BEAMLINE                       : I711
REMARK 200  X-RAY GENERATOR MODEL          : NULL; HOME SOURCE
REMARK 200  MONOCHROMATIC OR LAUE    (M/L) : M
REMARK 200  WAVELENGTH OR RANGE        (A) : 1.0526; 1.54
REMARK 200  MONOCHROMATOR                  : NULL
REMARK 200  OPTICS                         : NULL
REMARK 200
REMARK 200  DETECTOR TYPE                  : IMAGE PLATE; IMAGE PLATE
REMARK 200  DETECTOR MANUFACTURER          : MARRESEARCH; MARRESEARCH
REMARK 200  INTENSITY-INTEGRATION SOFTWARE : DENZO
REMARK 200  DATA SCALING SOFTWARE          : SCALEPACK
REMARK 200
REMARK 200  NUMBER OF UNIQUE REFLECTIONS   : 27881
REMARK 200  RESOLUTION RANGE HIGH      (A) : 2.000
REMARK 200  RESOLUTION RANGE LOW       (A) : 50.000
REMARK 200  REJECTION CRITERIA  (SIGMA(I)) : 0.000
REMARK 200
REMARK 200 OVERALL.
REMARK 200  COMPLETENESS FOR RANGE     (%) : 99.2
REMARK 200  DATA REDUNDANCY                : 5.900
```

Table 2


```
REMARK 200  R MERGE                          (I) : 0.03900
REMARK 200  R SYM                            (I) : 0.03900
REMARK 200  <I/SIGMA(I)> FOR THE DATA SET  : 19.6000
REMARK 200
REMARK 200 IN THE HIGHEST RESOLUTION SHELL.
REMARK 200  HIGHEST RESOLUTION SHELL, RANGE HIGH (A) : 2.00
REMARK 200  HIGHEST RESOLUTION SHELL, RANGE LOW  (A) : 2.07
REMARK 200  COMPLETENESS FOR SHELL      (%) : 99.4
REMARK 200  DATA REDUNDANCY IN SHELL        : 3.80
REMARK 200  R MERGE FOR SHELL           (I) : 0.20900
REMARK 200  R SYM FOR SHELL             (I) : 0.20900
REMARK 200  <I/SIGMA(I)> FOR SHELL          : 1.400
REMARK 200
REMARK 200 DIFFRACTION PROTOCOL: SINGLE WAVELENGTH
REMARK 200 METHOD USED TO DETERMINE THE STRUCTURE: MOLECULAR REPLACEMENT
REMARK 200 SOFTWARE USED: AMORE
REMARK 200 STARTING MODEL: PDB ENTRY 1EPF
REMARK 200
REMARK 200 REMARK: NULL
REMARK 280
REMARK 280 CRYSTAL
REMARK 280 SOLVENT CONTENT, VS   (%): NULL
REMARK 280 MATTHEWS COEFFICIENT, VM (ANGSTROMS**3/DA): NULL
REMARK 280
REMARK 280 CRYSTALLIZATION CONDITIONS: 14-17% PEG 4000, 450 MM LI SULFATE,
REMARK 280  100 MM NA ACETATE, PH 5.2, VAPOR DIFFUSION, HANGING DROP,
REMARK 280  TEMPERATURE 293K
REMARK 290
REMARK 290 CRYSTALLOGRAPHIC SYMMETRY
REMARK 290 SYMMETRY OPERATORS FOR SPACE GROUP: I 21 21 21
REMARK 290
REMARK 290      SYMOP   SYMMETRY
REMARK 290     NNNMMM   OPERATOR
REMARK 290       1555   X,Y,Z
REMARK 290       2555   1/2-X,-Y,1/2+Z
REMARK 290       3555   -X,1/2+Y,1/2-Z
REMARK 290       4555   1/2+X,1/2-Y,-Z
REMARK 290       5555   1/2+X,1/2+Y,1/2+Z
REMARK 290       6555   -X,1/2-Y,Z
REMARK 290       7555   1/2-X,Y,-Z
REMARK 290       8555   X,-Y,1/2-Z
REMARK 290
REMARK 290     WHERE NNN -> OPERATOR NUMBER
REMARK 290           MMM -> TRANSLATION VECTOR
REMARK 290
REMARK 290 CRYSTALLOGRAPHIC SYMMETRY TRANSFORMATIONS
REMARK 290 THE FOLLOWING TRANSFORMATIONS OPERATE ON THE ATOM/HETATM
REMARK 290 RECORDS IN THIS ENTRY TO PRODUCE CRYSTALLOGRAPHICALLY
REMARK 290 RELATED MOLECULES.
REMARK 290   SMTRY1   1  1.000000  0.000000  0.000000        0.00000
REMARK 290   SMTRY2   1  0.000000  1.000000  0.000000        0.00000
REMARK 290   SMTRY3   1  0.000000  0.000000  1.000000        0.00000
REMARK 290   SMTRY1   2 -1.000000  0.000000  0.000000       25.72000
REMARK 290   SMTRY2   2  0.000000 -1.000000  0.000000        0.00000
REMARK 290   SMTRY3   2  0.000000  0.000000  1.000000      -74.65000
REMARK 290   SMTRY1   3 -1.000000  0.000000  0.000000        0.00000
REMARK 290   SMTRY2   3  0.000000  1.000000  0.000000       53.88000
REMARK 290   SMTRY3   3  0.000000  0.000000 -1.000000       74.65000
REMARK 290   SMTRY1   4  1.000000  0.000000  0.000000       25.72000
```

```
REMARK 290   SMTRY2   4  0.000000 -1.000000  0.000000        53.88000
REMARK 290   SMTRY3   4  0.000000  0.000000 -1.000000         0.00000
REMARK 290   SMTRY1   5  1.000000  0.000000  0.000000        25.72000
REMARK 290   SMTRY2   5  0.000000  1.000000  0.000000        53.88000
REMARK 290   SMTRY3   5  0.000000  0.000000  1.000000        74.65000
REMARK 290   SMTRY1   6 -1.000000  0.000000  0.000000         0.00000
REMARK 290   SMTRY2   6  0.000000 -1.000000  0.000000        53.88000
REMARK 290   SMTRY3   6  0.000000  0.000000  1.000000         0.00000
REMARK 290   SMTRY1   7 -1.000000  0.000000  0.000000        25.72000
REMARK 290   SMTRY2   7  0.000000  1.000000  0.000000         0.00000
REMARK 290   SMTRY3   7  0.000000  0.000000 -1.000000         0.00000
REMARK 290   SMTRY1   8  1.000000  0.000000  0.000000         0.00000
REMARK 290   SMTRY2   8  0.000000 -1.000000  0.000000         0.00000
REMARK 290   SMTRY3   8  0.000000  0.000000 -1.000000        74.65000
REMARK 290
REMARK 290 REMARK: NULL
REMARK 300
REMARK 300 BIOMOLECULE: 1
REMARK 300 THIS ENTRY CONTAINS THE CRYSTALLOGRAPHIC ASYMMETRIC UNIT
REMARK 300 WHICH CONSISTS OF 1 CHAIN(S). SEE REMARK 350 FOR
REMARK 300 INFORMATION ON GENERATING THE BIOLOGICAL MOLECULE(S).
REMARK 350
REMARK 350 GENERATING THE BIOMOLECULE
REMARK 350 COORDINATES FOR A COMPLETE MULTIMER REPRESENTING THE KNOWN
REMARK 350 BIOLOGICALLY SIGNIFICANT OLIGOMERIZATION STATE OF THE
REMARK 350 MOLECULE CAN BE GENERATED BY APPLYING BIOMT TRANSFORMATIONS
REMARK 350 GIVEN BELOW.  BOTH NON-CRYSTALLOGRAPHIC AND
REMARK 350 CRYSTALLOGRAPHIC OPERATIONS ARE GIVEN.
REMARK 350
REMARK 350 BIOMOLECULE: 1
REMARK 350 APPLY THE FOLLOWING TO CHAINS: A
REMARK 350   BIOMT1   1  1.000000  0.000000  0.000000        0.00000
REMARK 350   BIOMT2   1  0.000000  1.000000  0.000000        0.00000
REMARK 350   BIOMT3   1  0.000000  0.000000  1.000000        0.00000
REMARK 465
REMARK 465 MISSING RESIDUES
REMARK 465 THE FOLLOWING RESIDUES WERE NOT LOCATED IN THE
REMARK 465 EXPERIMENT. (M=MODEL NUMBER; RES=RESIDUE NAME; C=CHAIN
REMARK 465 IDENTIFIER; SSSEQ=SEQUENCE NUMBER; I=INSERTION CODE.)
REMARK 465
REMARK 465   M RES C SSSEQI
REMARK 465     ARG A    -2
REMARK 465     GLU A   239
REMARK 465     GLU A   240
REMARK 500
REMARK 500 GEOMETRY AND STEREOCHEMISTRY
REMARK 500 SUBTOPIC: COVALENT BOND ANGLES
REMARK 500
REMARK 500 THE STEREOCHEMICAL PARAMETERS OF THE FOLLOWING RESIDUES
REMARK 500 HAVE VALUES WHICH DEVIATE FROM EXPECTED VALUES BY MORE
REMARK 500 THAN 6*RMSD (M=MODEL NUMBER; RES=RESIDUE NAME; C=CHAIN
REMARK 500 IDENTIFIER; SSEQ=SEQUENCE NUMBER; I=INSERTION CODE).
REMARK 500
REMARK 500 STANDARD TABLE:
REMARK 500 FORMAT: (10X,I3,1X,A3,1X,A1,I4,A1,3(1X,A4,2X),12X,F5.1)
REMARK 500
REMARK 500 EXPECTED VALUES: ENGH AND HUBER, 1991
REMARK 500
REMARK 500  M RES CSSEQI ATM1   ATM2   ATM3
```

```
REMARK 500   LEU A   1   N   -  CA  -  C   ANGL. DEV. = 11.0 DEGREES
REMARK 500   ASP A  27   N   -  CA  -  C   ANGL. DEV. = 11.4 DEGREES
REMARK 500   ALA A  28   N   -  CA  -  C   ANGL. DEV. =-17.5 DEGREES
REMARK 500   LYS A  29   N   -  CA  -  C   ANGL. DEV. = 12.7 DEGREES
REMARK 500   ASP A  56   N   -  CA  -  C   ANGL. DEV. =-11.4 DEGREES
REMARK 500   ALA A  89   N   -  CA  -  C   ANGL. DEV. =-10.5 DEGREES
REMARK 500   GLN A 108   N   -  CA  -  C   ANGL. DEV. =-10.5 DEGREES
REMARK 500   THR A 129   N   -  CA  -  C   ANGL. DEV. =-11.4 DEGREES
REMARK 500   ASP A 138   N   -  CA  -  C   ANGL. DEV. =-11.4 DEGREES
REMARK 500   ASP A 144   N   -  CA  -  C   ANGL. DEV. =-20.1 DEGREES
REMARK 500   THR A 194   N   -  CA  -  C   ANGL. DEV. =-11.0 DEGREES
REMARK 500   ARG A 257   N   -  CA  -  C   ANGL. DEV. = 17.3 DEGREES
REMARK 525
REMARK 525 SOLVENT
REMARK 525 THE FOLLOWING SOLVENT MOLECULES LIE FARTHER THAN EXPECTED
REMARK 525 FROM THE PROTEIN OR NUCLEIC ACID MOLECULE AND MAY BE
REMARK 525 ASSOCIATED WITH A SYMMETRY RELATED MOLECULE (M=MODEL
REMARK 525 NUMBER; RES=RESIDUE NAME; C=CHAIN IDENTIFIER; SSEQ=SEQUENCE
REMARK 525 NUMBER; I=INSERTION CODE):
REMARK 525
REMARK 525 M RES CSSEQI
REMARK 525     HOH     64         DISTANCE =  5.56 ANGSTROMS
REMARK 525     HOH     66         DISTANCE =  7.20 ANGSTROMS
REMARK 525     HOH     75         DISTANCE = 10.03 ANGSTROMS
REMARK 900
REMARK 900 RELATED ENTRIES
REMARK 900 RELATED ID: 2NCM   RELATED DB: PDB
REMARK 900 NMR STRUCTURE OF THE FIRST IMMUNOGLOBULIN DOMAIN OF THE
REMARK 900 NEURAL CELL ADHESION MOLECULE (NCAM)
REMARK 900 RELATED ID: 3NCM   RELATED DB: PDB
REMARK 900 NMR STRUCTURE OF THE SECOND IMMUNOGLOBULIN DOMAIN OF THE
REMARK 900 NEURAL CELL ADHESION MOLECULE (NCAM)
REMARK 900 RELATED ID: 1EPF   RELATED DB: PDB
REMARK 900 CRYSTAL STRUCTURE OF THE TWO N-TERMINAL IMMUNOGLOBULIN
REMARK 900 DOMAINS OF THE NEURAL CELL ADHESION MOLECULE (NCAM)
REMARK 999
REMARK 999 SEQUENCE
REMARK 999 RESIDUES -2, 239 AND 240 WERE NOT VISIBLE IN
REMARK 999 THE ELECTRON DENSITY.
DBREF  1QZ1 A    1   289  SWS    P13596   NCA1_RAT         20    308
SEQADV 1QZ1 ARG A   -2  SWS  P13596                 CLONING ARTIFACT
SEQADV 1QZ1 VAL A   -1  SWS  P13596                 CLONING ARTIFACT
SEQRES 1  A 291  ARG VAL LEU GLN VAL ASP ILE VAL PRO SER GLN GLY GLU
SEQRES 2  A 291  ILE SER VAL GLY GLU SER LYS PHE PHE LEU CYS GLN VAL
SEQRES 3  A 291  ALA GLY ASP ALA LYS ASP LYS ASP ILE SER TRP PHE SER
SEQRES 4  A 291  PRO ASN GLY GLU LYS LEU SER PRO ASN GLN GLN ARG ILE
SEQRES 5  A 291  SER VAL VAL TRP ASN ASP ASP SER SER THR LEU THR
SEQRES 6  A 291  ILE TYR ASN ALA ASN ILE ASP ASP ALA GLY ILE TYR LYS
SEQRES 7  A 291  CYS VAL VAL THR ALA GLU ASP GLY THR GLN SER GLU ALA
SEQRES 8  A 291  THR VAL ASN VAL LYS ILE PHE GLN LYS LEU MET PHE LYS
SEQRES 9  A 291  ASN ALA PRO THR PRO GLN GLU PHE LYS GLU GLY GLU ASP
SEQRES 10 A 291  ALA VAL ILE VAL CYS ASP VAL VAL SER SER LEU PRO PRO
SEQRES 11 A 291  THR ILE ILE TRP LYS HIS LYS GLY ARG ASP VAL ILE LEU
SEQRES 12 A 291  LYS LYS ASP VAL ARG PHE ILE VAL LEU SER ASN ASN TYR
SEQRES 13 A 291  LEU GLN ILE ARG GLY ILE LYS LYS THR ASP GLU GLY THR
SEQRES 14 A 291  TYR ARG CYS GLU GLY ARG ILE LEU ALA ARG GLY GLU ILE
SEQRES 15 A 291  ASN PHE LYS ASP ILE GLN VAL ILE VAL ASN VAL PRO PRO
SEQRES 16 A 291  THR VAL GLN ALA ARG GLN SER ILE VAL ASN ALA THR ALA
SEQRES 17 A 291  ASN LEU GLY GLN SER VAL THR LEU VAL CYS ASP ALA ASP
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Table 2


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SEQRES  18 A 291  GLY PHE PRO GLU PRO THR MET SER TRP THR LYS ASP GLY
SEQRES  19 A 291  GLU PRO ILE GLU ASN GLU GLU GLU ASP ASP GLU LYS HIS
SEQRES  20 A 291  ILE PHE SER ASP ASP SER SER GLU LEU THR ILE ARG ASN
SEQRES  21 A 291  VAL ASP LYS ASN ASP GLU ALA GLU TYR VAL CYS ILE ALA
SEQRES  22 A 291  GLU ASN LYS ALA GLY GLU GLN ASP ALA SER ILE HIS LEU
SEQRES  23 A 291  LYS VAL PHE ALA LYS
FORMUL   2  HOH    *265(H2 O1)
HELIX    1   1 ASN A   68  ALA A   72  5                                   5
HELIX    2   2 LYS A  161  GLU A  165  5                                   5
HELIX    3   3 ASP A  260  GLU A  264  5                                   5
SHEET    1   A 4 VAL A   3  VAL A   6  0
SHEET    2   A 4 LYS A  18  VAL A  24 -1  O  GLN A  23   N  ASP A   4
SHEET    3   A 4 SER A  59  ILE A  64 -1  O  ILE A  64   N  LYS A  18
SHEET    4   A 4 ILE A  50  ASP A  56 -1  N  VAL A  53   O  THR A  61
SHEET    1   B 4 GLY A  10  SER A  13  0
SHEET    2   B 4 GLN A  86  PHE A  96  1  O  LYS A  94   N  GLY A   0
SHEET    3   B 4 GLY A  73  THR A  80 -1  N  VAL A  79   O  SER A  87
SHEET    4   B 4 ASP A  32  PHE A  36 -1  N  SER A  34   O  VAL A  78
SHEET    1   C 2 MET A 100  ASN A 103  0
SHEET    2   C 2 ASP A 121  VAL A 123 -1  O  ASP A 121   N  ASN A 103
SHEET    1   D 4 GLN A 108  LYS A 111  0
SHEET    2   D 4 GLU A 179  ALA A 197  1  O  ASN A 190   N  PHE A 110
SHEET    3   D 4 GLY A 166  ILE A 174 -1  N  GLY A 166   O  VAL A 187
SHEET    4   D 4 THR A 129  HIS A 134 -1  N  LYS A 133   O  ARG A 169
SHEET    1   E 5 GLN A 108  LYS A 111  0
SHEET    2   E 5 GLU A 179  ALA A 197  1  O  ASN A 190   N  PHE A 110
SHEET    3   E 5 VAL A 212  PHE A 221 -1  O  ASP A 217   N  GLN A 196
SHEET    4   E 5 GLU A 253  ILE A 256 -1  O  LEU A 254   N  LEU A 214
SHEET    5   E 5 HIS A 245  PHE A 247 -1  N  ILE A 246   O  THR A 255
SHEET    1   F 3 ALA A 116  ILE A 118  0
SHEET    2   F 3 LEU A 155  ILE A 157 -1  O  ILE A 157   N  ALA A 116
SHEET    3   F 3 PHE A 147  VAL A 149 -1  N  ILE A 148   O  GLN A 156
SHEET    1   G 5 ILE A 201  THR A 205  0
SHEET    2   G 5 GLY A 276  PHE A 287  1  O  PHE A 287   N  ALA A 204
SHEET    3   G 5 ALA A 265  ASN A 273 -1  N  TYR A 267   O  ILE A 282
SHEET    4   G 5 THR A 225  LYS A 230 -1  N  SER A 227   O  ILE A 270
SHEET    5   G 5 GLU A 233  PRO A 234 -1  O  GLU A 233   N  LYS A 230
SSBOND   1 CYS A   22    CYS A   77
SSBOND   2 CYS A  120    CYS A  170
SSBOND   3 CYS A  216    CYS A  269
CISPEP   1 VAL A    6    PRO A    7          0        -0.41
CISPEP   2 THR A  106    PRO A  107          0        -0.64
CISPEP   3 PHE A  221    PRO A  222          0        -0.72
CRYST1   51.440  107.760  149.300  90.00  90.00  90.00 I 21 21 21   8
ORIGX1      1.000000  0.000000  0.000000        0.00000
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.019440  0.000000  0.000000        0.00000
SCALE2      0.000000  0.009280  0.000000        0.00000
SCALE3      0.000000  0.000000  0.006698        0.00000
ATOM      1  N   VAL A  -1      21.197  71.826 -24.060  1.00110.27 N
ATOM      2  CA  VAL A  -1      21.299  70.596 -24.891  1.00112.18 C
ATOM      3  C   VAL A  -1      20.583  69.411 -24.264  1.00111.88 C
ATOM      4  O   VAL A  -1      19.491  69.531 -23.699  1.00113.09 O
ATOM      5  CB  VAL A  -1      22.778  70.161 -25.114  1.00111.00 C
ATOM      6  CG1 VAL A  -1      23.591  71.324 -25.633  1.00109.72 C
ATOM      7  CG2 VAL A  -1      23.374  69.625 -23.817  1.00106.12 C
ATOM      8  N   LEU A   1      21.255  68.270 -24.364  1.00107.51 N
ATOM      9  CA  LEU A   1      20.778  66.981 -23.905  1.00100.28 C
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Table 2

ATOM	10	C	LEU	A	1	20.360	66.739	-22.465	1.00	94.24 C
ATOM	11	O	LEU	A	1	20.985	67.227	-21.518	1.00	93.77 O
ATOM	12	CB	LEU	A	1	21.808	65.936	-24.296	1.00	100.43 C
ATOM	13	CG	LEU	A	1	21.297	64.909	-25.303	1.00	103.11 C
ATOM	14	CD1	LEU	A	1	20.253	65.528	-26.233	1.00	106.65 C
ATOM	15	CD2	LEU	A	1	22.475	64.366	-26.088	1.00	101.88 C
ATOM	16	N	GLN	A	2	19.299	65.946	-22.328	1.00	87.47 N
ATOM	17	CA	GLN	A	2	18.771	65.575	-21.028	1.00	86.76 C
ATOM	18	C	GLN	A	2	18.937	64.075	-20.822	1.00	80.18 C
ATOM	19	O	GLN	A	2	18.520	63.264	-21.656	1.00	82.58 O
ATOM	20	CB	GLN	A	2	17.292	65.950	-20.902	1.00	89.86 C
ATOM	21	CG	GLN	A	2	16.819	65.996	-19.458	1.00	102.22 C
ATOM	22	CD	GLN	A	2	17.932	66.444	-18.500	1.00	109.49 C
ATOM	23	OE1	GLN	A	2	18.786	67.260	-18.859	1.00	112.97 O
ATOM	24	NE2	GLN	A	2	17.917	65.917	-17.275	1.00	110.51 N
ATOM	25	N	VAL	A	3	19.572	63.716	-19.714	1.00	68.44 N
ATOM	26	CA	VAL	A	3	19.790	62.317	-19.375	1.00	65.80 C
ATOM	27	C	VAL	A	3	19.290	62.058	-17.959	1.00	63.80 C
ATOM	28	O	VAL	A	3	19.588	62.816	-17.029	1.00	61.99 O
ATOM	29	CB	VAL	A	3	21.291	61.919	-19.495	1.00	70.09 C
ATOM	30	CG1	VAL	A	3	22.157	62.831	-18.653	1.00	66.37 C
ATOM	31	CG2	VAL	A	3	21.477	60.475	-19.072	1.00	53.43 C
ATOM	32	N	ASP	A	4	18.511	60.992	-17.807	1.00	59.47 N
ATOM	33	CA	ASP	A	4	17.957	60.635	-16.507	1.00	62.16 C
ATOM	34	C	ASP	A	4	18.056	59.137	-16.281	1.00	61.45 C
ATOM	35	O	ASP	A	4	17.973	58.337	-17.222	1.00	54.28 O
ATOM	36	CB	ASP	A	4	16.490	61.064	-16.410	1.00	57.25 C
ATOM	37	CG	ASP	A	4	16.312	62.564	-16.536	1.00	81.12 C
ATOM	38	OD1	ASP	A	4	16.784	63.302	-15.644	1.00	87.44 O
ATOM	39	OD2	ASP	A	4	15.702	63.010	-17.531	1.00	84.62 O
ATOM	40	N	ILE	A	5	18.226	58.760	-15.024	1.00	54.90 N
ATOM	41	CA	ILE	A	5	18.324	57.360	-14.692	1.00	47.24 C
ATOM	42	C	ILE	A	5	17.134	56.965	-13.832	1.00	49.02 C
ATOM	43	O	ILE	A	5	16.846	57.619	-12.826	1.00	47.37 O
ATOM	44	CB	ILE	A	5	19.625	57.077	-13.934	1.00	42.30 C
ATOM	45	CG1	ILE	A	5	20.823	57.333	-14.849	1.00	48.79 C
ATOM	46	CG2	ILE	A	5	19.638	55.615	-13.450	1.00	40.90 C
ATOM	47	CD1	ILE	A	5	22.158	57.356	-14.118	1.00	47.66 C
ATOM	48	N	VAL	A	6	16.445	55.900	-14.233	1.00	48.39 N
ATOM	49	CA	VAL	A	6	15.300	55.401	-13.480	1.00	48.78 C
ATOM	50	C	VAL	A	6	15.545	53.939	-13.119	1.00	52.24 C
ATOM	51	O	VAL	A	6	15.905	53.130	-13.980	1.00	51.37 O
ATOM	52	CB	VAL	A	6	14.008	55.484	-14.299	1.00	55.65 C
ATOM	53	CG1	VAL	A	6	12.857	54.882	-13.515	1.00	53.36 C
ATOM	54	CG2	VAL	A	6	13.712	56.928	-14.637	1.00	64.21 C
ATOM	55	N	PRO	A	7	15.418	53.594	-11.830	1.00	44.55 N
ATOM	56	CA	PRO	A	7	15.074	54.460	-10.692	1.00	44.98 C
ATOM	57	C	PRO	A	7	16.225	55.428	-10.411	1.00	52.07 C
ATOM	58	O	PRO	A	7	17.391	55.112	-10.662	1.00	47.92 O
ATOM	59	CB	PRO	A	7	14.842	53.462	-9.556	1.00	50.48 C
ATOM	60	CG	PRO	A	7	15.718	52.291	-9.944	1.00	45.69 C
ATOM	61	CD	PRO	A	7	15.446	52.181	-11.420	1.00	40.86 C
ATOM	62	N	SER	A	8	15.894	56.604	-9.893	1.00	46.31 N
ATOM	63	CA	SER	A	8	16.889	57.635	-9.634	1.00	49.55 C
ATOM	64	C	SER	A	8	17.921	57.250	-8.592	1.00	53.48 C
ATOM	65	O	SER	A	8	18.995	57.857	-8.515	1.00	54.87 O
ATOM	66	CB	SER	A	8	16.198	58.940	-9.236	1.00	55.09 C
ATOM	67	OG	SER	A	8	15.363	58.753	-8.111	1.00	61.93 O
ATOM	68	N	GLN	A	9	17.597	56.255	-7.776	1.00	46.60 N

Table 2

ATOM	69	CA	GLN	A	9	18.538	55.781	-6.771	1.00	47.40	C
ATOM	70	C	GLN	A	9	18.204	54.335	-6.448	1.00	44.46	C
ATOM	71	O	GLN	A	9	17.103	53.864	-6.739	1.00	52.34	O
ATOM	72	CB	GLN	A	9	18.494	56.658	-5.515	1.00	58.55	C
ATOM	73	CG	GLN	A	9	17.103	56.860	-4.900	1.00	65.92	C
ATOM	74	CD	GLN	A	9	17.149	57.765	-3.665	1.00	81.94	C
ATOM	75	OE1	GLN	A	9	17.878	57.484	-2.713	1.00	86.13	O
ATOM	76	NE2	GLN	A	9	16.374	58.853	-3.678	1.00	82.96	N
ATOM	77	N	GLY	A	10	19.157	53.606	-5.883	1.00	46.46	N
ATOM	78	CA	GLY	A	10	18.868	52.215	-5.589	1.00	50.99	C
ATOM	79	C	GLY	A	10	19.637	51.600	-4.442	1.00	48.97	C
ATOM	80	O	GLY	A	10	20.719	52.048	-4.070	1.00	46.47	O
ATOM	81	N	GLU	A	11	19.051	50.559	-3.871	1.00	54.04	N
ATOM	82	CA	GLU	A	11	19.684	49.842	-2.778	1.00	54.83	C
ATOM	83	C	GLU	A	11	19.560	48.362	-3.127	1.00	47.65	C
ATOM	84	O	GLU	A	11	18.499	47.918	-3.557	1.00	47.49	O
ATOM	85	CB	GLU	A	11	18.970	50.150	-1.456	1.00	49.30	C
ATOM	86	CG	GLU	A	11	19.627	49.508	-0.255	1.00	67.71	C
ATOM	87	CD	GLU	A	11	19.026	49.974	1.061	1.00	68.83	C
ATOM	88	OE1	GLU	A	11	17.829	49.704	1.305	1.00	70.78	O
ATOM	89	OE2	GLU	A	11	19.758	50.620	1.843	1.00	73.96	O
ATOM	90	N	ILE	A	12	20.636	47.599	-2.965	1.00	44.79	N
ATOM	91	CA	ILE	A	12	20.587	46.178	-3.302	1.00	43.25	C
ATOM	92	C	ILE	A	12	21.164	45.332	-2.185	1.00	49.76	C
ATOM	93	O	ILE	A	12	22.261	45.610	-1.692	1.00	45.49	O
ATOM	94	CB	ILE	A	12	21.402	45.856	-4.562	1.00	46.25	C
ATOM	95	CG1	ILE	A	12	21.182	46.938	-5.621	1.00	48.07	C
ATOM	96	CG2	ILE	A	12	20.984	44.481	-5.114	1.00	40.48	C
ATOM	97	CD1	ILE	A	12	22.125	46.814	-6.795	1.00	44.46	C
ATOM	98	N	SER	A	13	20.421	44.296	-1.796	1.00	50.25	N
ATOM	99	CA	SER	A	13	20.880	43.384	-0.755	1.00	49.85	C
ATOM	100	C	SER	A	13	21.869	42.416	-1.385	1.00	41.84	C
ATOM	101	O	SER	A	13	21.690	41.973	-2.526	1.00	43.99	O
ATOM	102	CB	SER	A	13	19.707	42.608	-0.156	1.00	48.85	C
ATOM	103	OG	SER	A	13	20.157	41.794	0.916	1.00	55.47	O
ATOM	104	N	VAL	A	14	22.926	42.114	-0.644	1.00	50.09	N
ATOM	105	CA	VAL	A	14	23.955	41.214	-1.126	1.00	48.58	C
ATOM	106	C	VAL	A	14	23.358	39.962	-1.742	1.00	53.11	C
ATOM	107	O	VAL	A	14	22.481	39.320	-1.165	1.00	54.25	O
ATOM	108	CB	VAL	A	14	24.924	40.814	0.004	1.00	51.58	C
ATOM	109	CG1	VAL	A	14	25.880	39.739	-0.479	1.00	51.54	C
ATOM	110	CG2	VAL	A	14	25.702	42.027	0.455	1.00	51.93	C
ATOM	111	N	GLY	A	15	23.841	39.636	-2.935	1.00	45.67	N
ATOM	112	CA	GLY	A	15	23.367	38.471	-3.643	1.00	45.80	C
ATOM	113	C	GLY	A	15	22.174	38.738	-4.546	1.00	49.51	C
ATOM	114	O	GLY	A	15	21.845	37.910	-5.395	1.00	44.42	O
ATOM	115	N	GLU	A	16	21.516	39.885	-4.390	1.00	48.69	N
ATOM	116	CA	GLU	A	16	20.360	40.167	-5.239	1.00	44.66	C
ATOM	117	C	GLU	A	16	20.712	41.010	-6.459	1.00	38.83	C
ATOM	118	O	GLU	A	16	21.874	41.355	-6.672	1.00	41.87	O
ATOM	119	CB	GLU	A	16	19.239	40.800	-4.403	1.00	44.40	C
ATOM	120	CG	GLU	A	16	18.799	39.848	-3.289	1.00	57.20	C
ATOM	121	CD	GLU	A	16	17.666	40.373	-2.428	1.00	67.70	C
ATOM	122	OE1	GLU	A	16	17.111	41.448	-2.739	1.00	72.10	O
ATOM	123	OE2	GLU	A	16	17.328	39.695	-1.433	1.00	77.10	O
ATOM	124	N	SER	A	17	19.712	41.319	-7.274	1.00	38.10	N
ATOM	125	CA	SER	A	17	19.950	42.068	-8.496	1.00	39.72	C
ATOM	126	C	SER	A	17	19.039	43.283	-8.655	1.00	43.71	C
ATOM	127	O	SER	A	17	17.960	43.330	-8.074	1.00	48.43	O

Table 2

ATOM	128	CB	SER	A	17	19.787	41.125	-9.694	1.00	42.04 C
ATOM	129	OG	SER	A	17	20.672	40.016	-9.592	1.00	49.33 O
ATOM	130	N	LYS	A	18	19.491	44.273	-9.427	1.00	39.31 N
ATOM	131	CA	LYS	A	18	18.725	45.495	-9.689	1.00	40.44 C
ATOM	132	C	LYS	A	18	19.194	46.068	-11.004	1.00	36.17 C
ATOM	133	O	LYS	A	18	20.310	45.799	-11.447	1.00	41.18 O
ATOM	134	CB	LYS	A	18	18.944	46.552	-8.603	1.00	45.93 C
ATOM	135	CG	LYS	A	18	17.902	46.558	-7.506	1.00	63.96 C
ATOM	136	CD	LYS	A	18	17.343	47.954	-7.318	1.00	77.99 C
ATOM	137	CE	LYS	A	18	16.408	48.029	-6.120	1.00	91.67 C
ATOM	138	NZ	LYS	A	18	15.285	47.049	-6.198	1.00	104.95 N
ATOM	139	N	PHE	A	19	18.355	46.866	-11.632	1.00	39.73 N
ATOM	140	CA	PHE	A	19	18.758	47.445	-12.889	1.00	42.56 C
ATOM	141	C	PHE	A	19	18.382	48.903	-12.907	1.00	45.52 C
ATOM	142	O	PHE	A	19	17.535	49.352	-12.123	1.00	41.88 O
ATOM	143	CB	PHE	A	19	18.131	46.681	-14.058	1.00	37.12 C
ATOM	144	CG	PHE	A	19	16.658	46.890	-14.220	1.00	41.51 C
ATOM	145	CD1	PHE	A	19	16.175	47.864	-15.090	1.00	45.13 C
ATOM	146	CD2	PHE	A	19	15.742	46.075	-13.547	1.00	42.50 C
ATOM	147	CE1	PHE	A	19	14.794	48.006	-15.310	1.00	44.84 C
ATOM	148	CE2	PHE	A	19	14.377	46.212	-13.759	1.00	43.30 C
ATOM	149	CZ	PHE	A	19	13.899	47.182	-14.639	1.00	41.52 C
ATOM	150	N	PHE	A	20	19.020	49.637	-13.813	1.00	37.54 N
ATOM	151	CA	PHE	A	20	18.816	51.062	-13.938	1.00	38.86 C
ATOM	152	C	PHE	A	20	18.816	51.437	-15.408	1.00	46.44 C
ATOM	153	O	PHE	A	20	19.702	51.035	-16.165	1.00	47.88 O
ATOM	154	CB	PHE	A	20	19.948	51.798	-13.205	1.00	36.96 C
ATOM	155	CG	PHE	A	20	20.112	51.368	-11.784	1.00	46.76 C
ATOM	156	CD1	PHE	A	20	20.904	50.267	-11.460	1.00	48.63 C
ATOM	157	CD2	PHE	A	20	19.427	52.027	-10.765	1.00	42.55 C
ATOM	158	CE1	PHE	A	20	21.008	49.826	-10.138	1.00	46.86 C
ATOM	159	CE2	PHE	A	20	19.525	51.591	-9.436	1.00	40.53 C
ATOM	160	CZ	PHE	A	20	20.317	50.489	-9.126	1.00	44.32 C
ATOM	161	N	LEU	A	21	17.816	52.209	-15.806	1.00	46.01 N
ATOM	162	CA	LEU	A	21	17.680	52.649	-17.189	1.00	49.63 C
ATOM	163	C	LEU	A	21	18.131	54.087	-17.360	1.00	46.97 C
ATOM	164	O	LEU	A	21	17.602	54.990	-16.719	1.00	43.22 O
ATOM	165	CB	LEU	A	21	16.218	52.530	-17.641	1.00	54.55 C
ATOM	166	CG	LEU	A	21	15.857	53.049	-19.040	1.00	57.21 C
ATOM	167	CD1	LEU	A	21	16.625	52.281	-20.096	1.00	58.14 C
ATOM	168	CD2	LEU	A	21	14.365	52.891	-19.274	1.00	55.27 C
ATOM	169	N	CYS	A	22	19.122	54.291	-18.218	1.00	46.45 N
ATOM	170	CA	CYS	A	22	19.615	55.628	-18.506	1.00	48.52 C
ATOM	171	C	CYS	A	22	18.920	56.056	-19.788	1.00	54.42 C
ATOM	172	O	CYS	A	22	19.157	55.478	-20.848	1.00	51.82 O
ATOM	173	CB	CYS	A	22	21.115	55.601	-18.730	1.00	49.72 C
ATOM	174	SG	CYS	A	22	21.827	57.215	-19.167	1.00	55.16 S
ATOM	175	N	GLN	A	23	18.069	57.071	-19.689	1.00	59.11 N
ATOM	176	CA	GLN	A	23	17.312	57.546	-20.837	1.00	66.68 C
ATOM	177	C	GLN	A	23	17.718	58.941	-21.314	1.00	63.21 C
ATOM	178	O	GLN	A	23	17.951	59.839	-20.509	1.00	57.50 O
ATOM	179	CB	GLN	A	23	15.825	57.547	-20.482	1.00	69.27 C
ATOM	180	CG	GLN	A	23	14.900	57.940	-21.618	1.00	83.38 C
ATOM	181	CD	GLN	A	23	14.575	56.779	-22.549	1.00	90.68 C
ATOM	182	OE1	GLN	A	23	14.251	55.685	-22.089	1.00	97.59 O
ATOM	183	NE2	GLN	A	23	14.642	57.016	-23.861	1.00	95.34 N
ATOM	184	N	VAL	A	24	17.799	59.118	-22.629	1.00	67.26 N
ATOM	185	CA	VAL	A	24	18.145	60.415	-23.197	1.00	74.82 C
ATOM	186	C	VAL	A	24	16.857	61.028	-23.739	1.00	75.90 C

Table 2

ATOM	187	O	VAL	A	24	16.039	60.338	-24.356	1.00	76.41 O
ATOM	188	CB	VAL	A	24	19.178	60.285	-24.343	1.00	77.43 C
ATOM	189	CG1	VAL	A	24	19.560	61.657	-24.852	1.00	77.38 C
ATOM	190	CG2	VAL	A	24	20.418	59.547	-23.856	1.00	81.07 C
ATOM	191	N	ALA	A	25	16.685	62.324	-23.500	1.00	82.73 N
ATOM	192	CA	ALA	A	25	15.490	63.053	-23.933	1.00	92.22 C
ATOM	193	C	ALA	A	25	15.455	63.428	-25.424	1.00	99.21 C
ATOM	194	O	ALA	A	25	16.491	63.734	-26.019	1.00	99.63 O
ATOM	195	CB	ALA	A	25	15.326	64.307	-23.078	1.00	89.44 C
ATOM	196	N	GLY	A	26	14.249	63.405	-26.002	1.00	107.66 N
ATOM	197	CA	GLY	A	26	14.040	63.735	-27.410	1.00	117.13 C
ATOM	198	C	GLY	A	26	14.697	62.739	-28.348	1.00	123.74 C
ATOM	199	O	GLY	A	26	14.060	62.088	-29.188	1.00	126.85 O
ATOM	200	N	ASP	A	27	16.010	62.671	-28.187	1.00	127.93 N
ATOM	201	CA	ASP	A	27	16.915	61.795	-28.897	1.00	131.73 C
ATOM	202	C	ASP	A	27	17.049	61.809	-30.410	1.00	132.38 C
ATOM	203	O	ASP	A	27	16.518	60.944	-31.112	1.00	134.43 O
ATOM	204	CB	ASP	A	27	16.721	60.353	-28.433	1.00	133.67 C
ATOM	205	CG	ASP	A	27	17.976	59.540	-28.620	1.00	136.05 C
ATOM	206	OD1	ASP	A	27	19.011	60.177	-28.888	1.00	137.46 O
ATOM	207	OD2	ASP	A	27	17.940	58.305	-28.501	1.00	138.22 O
ATOM	208	N	ALA	A	28	17.776	62.812	-30.894	1.00	130.01 N
ATOM	209	CA	ALA	A	28	18.098	62.888	-32.301	1.00	127.19 C
ATOM	210	C	ALA	A	28	19.203	61.826	-32.208	1.00	125.97 C
ATOM	211	O	ALA	A	28	19.562	61.453	-31.091	1.00	125.76 O
ATOM	212	CB	ALA	A	28	18.672	64.248	-32.657	1.00	123.21 C
ATOM	213	N	LYS	A	29	19.777	61.332	-33.300	1.00	124.23 N
ATOM	214	CA	LYS	A	29	20.754	60.267	-33.095	1.00	120.04 C
ATOM	215	C	LYS	A	29	22.237	60.419	-33.356	1.00	114.93 C
ATOM	216	O	LYS	A	29	22.773	61.503	-33.593	1.00	109.02 O
ATOM	217	CB	LYS	A	29	20.254	58.988	-33.777	1.00	124.97 C
ATOM	218	CG	LYS	A	29	19.095	58.340	-33.030	1.00	125.66 C
ATOM	219	CD	LYS	A	29	18.639	57.047	-33.674	1.00	125.32 C
ATOM	220	CE	LYS	A	29	17.462	56.460	-32.915	1.00	120.15 C
ATOM	221	NZ	LYS	A	29	16.388	57.477	-32.740	1.00	120.03 N
ATOM	222	N	ASP	A	30	22.875	59.260	-33.286	1.00	110.94 N
ATOM	223	CA	ASP	A	30	24.297	59.108	-33.440	1.00	108.72 C
ATOM	224	C	ASP	A	30	25.004	59.738	-32.257	1.00	102.56 C
ATOM	225	O	ASP	A	30	25.869	60.592	-32.425	1.00	101.55 O
ATOM	226	CB	ASP	A	30	24.800	59.729	-34.740	1.00	114.65 C
ATOM	227	CG	ASP	A	30	25.573	58.735	-35.584	1.00	121.84 C
ATOM	228	OD1	ASP	A	30	26.219	57.833	-35.001	1.00	126.50 O
ATOM	229	OD2	ASP	A	30	25.543	58.853	-36.824	1.00	125.16 O
ATOM	230	N	LYS	A	31	24.602	59.339	-31.055	1.00	90.62 N
ATOM	231	CA	LYS	A	31	25.252	59.820	-29.845	1.00	86.82 C
ATOM	232	C	LYS	A	31	25.645	58.547	-29.120	1.00	76.37 C
ATOM	233	O	LYS	A	31	25.000	57.512	-29.280	1.00	76.59 O
ATOM	234	CB	LYS	A	31	24.315	60.658	-28.965	1.00	87.55 C
ATOM	235	CG	LYS	A	31	23.238	59.873	-28.261	1.00	90.62 C
ATOM	236	CD	LYS	A	31	21.906	60.210	-28.856	1.00	90.82 C
ATOM	237	CE	LYS	A	31	21.081	58.968	-28.999	1.00	94.15 C
ATOM	238	NZ	LYS	A	31	20.424	58.901	-30.339	1.00	96.17 N
ATOM	239	N	ASP	A	32	26.711	58.620	-28.341	1.00	66.33 N
ATOM	240	CA	ASP	A	32	27.202	57.467	-27.607	1.00	64.69 C
ATOM	241	C	ASP	A	32	26.732	57.503	-26.163	1.00	57.45 C
ATOM	242	O	ASP	A	32	26.707	58.563	-25.532	1.00	61.27 O
ATOM	243	CB	ASP	A	32	28.740	57.448	-27.669	1.00	59.49 C
ATOM	244	CG	ASP	A	32	29.372	56.362	-26.791	1.00	67.93 C
ATOM	245	OD1	ASP	A	32	29.627	56.626	-25.589	1.00	51.53 O

ATOM	246	OD2	ASP	A	32	29.626	55.248	-27.308	1.00	61.79	O
ATOM	247	N	ILE	A	33	26.336	56.342	-25.657	1.00	54.91	N
ATOM	248	CA	ILE	A	33	25.911	56.210	-24.271	1.00	52.46	C
ATOM	249	C	ILE	A	33	26.823	55.173	-23.640	1.00	53.58	C
ATOM	250	O	ILE	A	33	26.875	54.022	-24.083	1.00	50.96	O
ATOM	251	CB	ILE	A	33	24.470	55.712	-24.139	1.00	51.31	C
ATOM	252	CG1	ILE	A	33	23.518	56.700	-24.800	1.00	52.96	C
ATOM	253	CG2	ILE	A	33	24.116	55.563	-22.654	1.00	50.09	C
ATOM	254	CD1	ILE	A	33	22.087	56.233	-24.828	1.00	54.31	C
ATOM	255	N	SER	A	34	27.535	55.588	-22.603	1.00	43.80	N
ATOM	256	CA	SER	A	34	28.463	54.716	-21.910	1.00	47.69	C
ATOM	257	C	SER	A	34	28.262	54.831	-20.410	1.00	51.46	C
ATOM	258	O	SER	A	34	27.899	55.892	-19.897	1.00	50.26	O
ATOM	259	CB	SER	A	34	29.898	55.105	-22.255	1.00	44.86	C
ATOM	260	OG	SER	A	34	30.197	54.768	-23.592	1.00	56.99	O
ATOM	261	N	TRP	A	35	28.488	53.726	-19.714	1.00	47.72	N
ATOM	262	CA	TRP	A	35	28.359	53.713	-18.270	1.00	42.75	C
ATOM	263	C	TRP	A	35	29.741	53.598	-17.652	1.00	45.12	C
ATOM	264	O	TRP	A	35	30.640	52.967	-18.223	1.00	44.07	O
ATOM	265	CB	TRP	A	35	27.511	52.531	-17.800	1.00	39.02	C
ATOM	266	CG	TRP	A	35	26.028	52.667	-18.015	1.00	43.96	C
ATOM	267	CD1	TRP	A	35	25.323	52.308	-19.126	1.00	38.82	C
ATOM	268	CD2	TRP	A	35	25.062	53.080	-17.041	1.00	36.18	C
ATOM	269	NE1	TRP	A	35	23.974	52.454	-18.901	1.00	45.99	N
ATOM	270	CE2	TRP	A	35	23.786	52.925	-17.632	1.00	47.03	C
ATOM	271	CE3	TRP	A	35	25.150	53.556	-15.735	1.00	39.81	C
ATOM	272	CZ2	TRP	A	35	22.605	53.232	-16.948	1.00	43.25	C
ATOM	273	CZ3	TRP	A	35	23.962	53.865	-15.054	1.00	41.38	C
ATOM	274	CH2	TRP	A	35	22.713	53.699	-15.668	1.00	42.80	C
ATOM	275	N	PHE	A	36	29.907	54.225	-16.491	1.00	45.19	N
ATOM	276	CA	PHE	A	36	31.160	54.178	-15.748	1.00	44.89	C
ATOM	277	C	PHE	A	36	30.834	53.716	-14.345	1.00	44.82	C
ATOM	278	O	PHE	A	36	29.858	54.166	-13.755	1.00	41.52	O
ATOM	279	CB	PHE	A	36	31.819	55.556	-15.675	1.00	43.10	C
ATOM	280	CG	PHE	A	36	32.286	56.062	-17.006	1.00	55.53	C
ATOM	281	CD1	PHE	A	36	31.385	56.639	-17.893	1.00	51.14	C
ATOM	282	CD2	PHE	A	36	33.610	55.883	-17.407	1.00	46.89	C
ATOM	283	CE1	PHE	A	36	31.789	57.030	-19.173	1.00	54.91	C
ATOM	284	CE2	PHE	A	36	34.030	56.269	-18.684	1.00	55.64	C
ATOM	285	CZ	PHE	A	36	33.110	56.846	-19.573	1.00	50.29	C
ATOM	286	N	SER	A	37	31.641	52.795	-13.832	1.00	42.90	N
ATOM	287	CA	SER	A	37	31.447	52.289	-12.488	1.00	52.59	C
ATOM	288	C	SER	A	37	31.973	53.321	-11.490	1.00	53.66	C
ATOM	289	O	SER	A	37	32.581	54.325	-11.878	1.00	46.56	O
ATOM	290	CB	SER	A	37	32.176	50.950	-12.322	1.00	56.49	C
ATOM	291	OG	SER	A	37	33.540	51.055	-12.675	1.00	54.60	O
ATOM	292	N	PRO	A	38	31.729	53.096	-10.192	1.00	55.82	N
ATOM	293	CA	PRO	A	38	32.169	54.004	-9.124	1.00	58.18	C
ATOM	294	C	PRO	A	38	33.682	54.241	-9.057	1.00	56.07	C
ATOM	295	O	PRO	A	38	34.135	55.248	-8.519	1.00	57.12	O
ATOM	296	CB	PRO	A	38	31.619	53.338	-7.864	1.00	55.81	C
ATOM	297	CG	PRO	A	38	30.327	52.731	-8.377	1.00	51.53	C
ATOM	298	CD	PRO	A	38	30.764	52.107	-9.677	1.00	50.32	C
ATOM	299	N	ASN	A	39	34.456	53.317	-9.609	1.00	52.69	N
ATOM	300	CA	ASN	A	39	35.905	53.452	-9.613	1.00	59.02	C
ATOM	301	C	ASN	A	39	36.396	54.175	-10.881	1.00	61.73	C
ATOM	302	O	ASN	A	39	37.585	54.160	-11.188	1.00	57.13	O
ATOM	303	CB	ASN	A	39	36.551	52.077	-9.523	1.00	56.75	C
ATOM	304	CG	ASN	A	39	36.432	51.310	-10.810	1.00	71.38	C

ATOM	305	OD1	ASN	A	39	35.531	51.565	-11.603	1.00	73.88	O
ATOM	306	ND2	ASN	A	39	37.332	50.361	-11.027	1.00	79.44	N
ATOM	307	N	GLY	A	40	35.471	54.777	-11.626	1.00	54.18	N
ATOM	308	CA	GLY	A	40	35.839	55.523	-12.825	1.00	58.26	C
ATOM	309	C	GLY	A	40	36.049	54.777	-14.126	1.00	56.72	C
ATOM	310	O	GLY	A	40	36.311	55.385	-15.161	1.00	59.14	O
ATOM	311	N	GLU	A	41	35.940	53.462	-14.098	1.00	53.24	N
ATOM	312	CA	GLU	A	41	36.137	52.712	-15.312	1.00	54.15	C
ATOM	313	C	GLU	A	41	34.887	52.572	-16.152	1.00	52.64	C
ATOM	314	O	GLU	A	41	33.772	52.444	-15.645	1.00	51.92	O
ATOM	315	CB	GLU	A	41	36.695	51.341	-14.988	1.00	62.00	C
ATOM	316	CG	GLU	A	41	38.100	51.410	-14.451	1.00	86.56	C
ATOM	317	CD	GLU	A	41	38.565	50.074	-13.931	1.00	94.84	C
ATOM	318	OE1	GLU	A	41	37.901	49.059	-14.243	1.00	99.92	O
ATOM	319	OE2	GLU	A	41	39.591	50.041	-13.220	1.00	98.17	O
ATOM	320	N	LYS	A	42	35.104	52.625	-17.457	1.00	48.52	N
ATOM	321	CA	LYS	A	42	34.050	52.475	-18.430	1.00	45.24	C
ATOM	322	C	LYS	A	42	33.714	50.979	-18.477	1.00	52.84	C
ATOM	323	O	LYS	A	42	34.607	50.126	-18.534	1.00	47.42	O
ATOM	324	CB	LYS	A	42	34.536	52.971	-19.796	1.00	46.19	C
ATOM	325	CG	LYS	A	42	33.502	52.863	-20.930	1.00	58.73	C
ATOM	326	CD	LYS	A	42	34.006	53.553	-22.205	1.00	60.30	C
ATOM	327	CE	LYS	A	42	33.004	53.446	-23.353	1.00	69.24	C
ATOM	328	NZ	LYS	A	42	33.486	54.104	-24.606	1.00	73.95	N
ATOM	329	N	LEU	A	43	32.425	50.659	-18.441	1.00	42.58	N
ATOM	330	CA	LEU	A	43	31.986	49.270	-18.453	1.00	44.33	C
ATOM	331	C	LEU	A	43	31.907	48.724	-19.863	1.00	45.36	C
ATOM	332	O	LEU	A	43	31.315	49.351	-20.734	1.00	49.42	O
ATOM	333	CB	LEU	A	43	30.613	49.177	-17.778	1.00	37.59	C
ATOM	334	CG	LEU	A	43	30.672	49.579	-16.302	1.00	45.02	C
ATOM	335	CD1	LEU	A	43	29.276	49.708	-15.713	1.00	48.59	C
ATOM	336	CD2	LEU	A	43	31.489	48.538	-15.550	1.00	45.09	C
ATOM	337	N	SER	A	44	32.507	47.566	-20.100	0.50	34.43	N
ATOM	338	CA	SER	A	44	32.436	46.990	-21.429	0.50	37.54	C
ATOM	339	C	SER	A	44	31.017	46.509	-21.595	0.50	40.70	C
ATOM	340	O	SER	A	44	30.404	45.984	-20.672	0.50	31.07	O
ATOM	341	CB	SER	A	44	33.394	45.813	-21.590	0.50	34.76	C
ATOM	342	OG	SER	A	44	34.730	46.238	-21.418	0.50	37.63	O
ATOM	343	N	PRO	A	45	30.475	46.684	-22.787	1.00	55.79	N
ATOM	344	CA	PRO	A	45	29.104	46.261	-23.062	1.00	56.53	C
ATOM	345	C	PRO	A	45	28.910	44.761	-23.041	1.00	53.37	C
ATOM	346	O	PRO	A	45	29.849	43.986	-23.229	1.00	56.21	O
ATOM	347	CB	PRO	A	45	28.836	46.833	-24.458	1.00	60.37	C
ATOM	348	CG	PRO	A	45	29.823	47.960	-24.586	1.00	60.02	C
ATOM	349	CD	PRO	A	45	31.056	47.392	-23.941	1.00	63.21	C
ATOM	350	N	ASN	A	46	27.667	44.370	-22.800	1.00	57.48	N
ATOM	351	CA	ASN	A	46	27.279	42.973	-22.812	1.00	57.72	C
ATOM	352	C	ASN	A	46	28.150	41.993	-22.017	1.00	57.75	C
ATOM	353	O	ASN	A	46	28.534	40.950	-22.541	1.00	60.65	O
ATOM	354	CB	ASN	A	46	27.179	42.508	-24.272	1.00	67.80	C
ATOM	355	CG	ASN	A	46	26.285	43.417	-25.119	1.00	71.96	C
ATOM	356	OD1	ASN	A	46	25.090	43.557	-24.850	1.00	81.33	O
ATOM	357	ND2	ASN	A	46	26.862	44.033	-26.146	1.00	70.84	N
ATOM	358	N	GLN	A	47	28.478	42.325	-20.771	1.00	53.34	N
ATOM	359	CA	GLN	A	47	29.250	41.408	-19.925	1.00	49.41	C
ATOM	360	C	GLN	A	47	28.202	40.672	-19.091	1.00	50.32	C
ATOM	361	O	GLN	A	47	27.029	41.040	-19.111	1.00	47.47	O
ATOM	362	CB	GLN	A	47	30.232	42.156	-19.022	1.00	51.46	C
ATOM	363	CG	GLN	A	47	31.291	42.936	-19.798	1.00	49.02	C

Table 2

ATOM	364	CD	GLN	A	47	32.023	42.055	-20.812	1.00	60.54 C
ATOM	365	OE1	GLN	A	47	32.910	41.286	-20.448	1.00	52.30 O
ATOM	366	NE2	GLN	A	47	31.634	42.149	-22.082	1.00	51.19 N
ATOM	367	N	GLN	A	48	28.630	39.669	-18.336	1.00	52.29 N
ATOM	368	CA	GLN	A	48	27.728	38.807	-17.566	1.00	56.49 C
ATOM	369	C	GLN	A	48	27.049	39.337	-16.305	1.00	58.23 C
ATOM	370	O	GLN	A	48	25.818	39.453	-16.238	1.00	50.89 O
ATOM	371	CB	GLN	A	48	28.486	37.524	-17.199	1.00	69.79 C
ATOM	372	CG	GLN	A	48	27.606	36.324	-16.903	1.00	85.42 C
ATOM	373	CD	GLN	A	48	27.071	35.675	-18.172	1.00	96.52 C
ATOM	374	OE1	GLN	A	48	27.848	35.302	-19.052	1.00	103.65 O
ATOM	375	NE2	GLN	A	48	25.745	35.530	-18.272	1.00	97.26 N
ATOM	376	N	ARG	A	49	27.866	39.613	-15.297	1.00	46.27 N
ATOM	377	CA	ARG	A	49	27.376	40.069	-14.009	1.00	49.02 C
ATOM	378	C	ARG	A	49	27.031	41.558	-13.965	1.00	50.34 C
ATOM	379	O	ARG	A	49	25.951	41.929	-13.518	1.00	44.46 O
ATOM	380	CB	ARG	A	49	28.404	39.724	-12.937	1.00	43.05 C
ATOM	381	CG	ARG	A	49	27.841	39.691	-11.541	1.00	50.00 C
ATOM	382	CD	ARG	A	49	28.920	39.301	-10.560	1.00	46.14 C
ATOM	383	NE	ARG	A	49	29.847	40.402	-10.332	1.00	50.29 N
ATOM	384	CZ	ARG	A	49	29.552	41.479	-9.614	1.00	49.75 C
ATOM	385	NH1	ARG	A	49	28.355	41.602	-9.054	1.00	46.61 N
ATOM	386	NH2	ARG	A	49	30.456	42.434	-9.450	1.00	54.16 N
ATOM	387	N	ILE	A	50	27.950	42.413	-14.404	1.00	45.13 N
ATOM	388	CA	ILE	A	50	27.693	43.846	-14.431	1.00	47.45 C
ATOM	389	C	ILE	A	50	27.362	44.081	-15.886	1.00	49.10 C
ATOM	390	O	ILE	A	50	28.236	44.288	-16.718	1.00	46.05 O
ATOM	391	CB	ILE	A	50	28.927	44.633	-13.989	1.00	46.67 C
ATOM	392	CG1	ILE	A	50	29.309	44.197	-12.569	1.00	49.39 C
ATOM	393	CG2	ILE	A	50	28.645	46.122	-14.047	1.00	45.96 C
ATOM	394	CD1	ILE	A	50	28.175	44.305	-11.547	1.00	38.44 C
ATOM	395	N	SER	A	51	26.069	44.019	-16.172	1.00	45.97 N
ATOM	396	CA	SER	A	51	25.572	44.111	-17.523	1.00	42.85 C
ATOM	397	C	SER	A	51	25.123	45.464	-18.027	1.00	47.59 C
ATOM	398	O	SER	A	51	24.300	46.145	-17.408	1.00	47.20 O
ATOM	399	CB	SER	A	51	24.430	43.096	-17.676	1.00	42.67 C
ATOM	400	OG	SER	A	51	23.643	43.375	-18.811	1.00	55.89 O
ATOM	401	N	VAL	A	52	25.689	45.856	-19.159	1.00	45.49 N
ATOM	402	CA	VAL	A	52	25.317	47.100	-19.802	1.00	46.68 C
ATOM	403	C	VAL	A	52	24.768	46.706	-21.155	1.00	52.16 C
ATOM	404	O	VAL	A	52	25.483	46.140	-21.991	1.00	52.43 O
ATOM	405	CB	VAL	A	52	26.504	48.038	-20.028	1.00	51.87 C
ATOM	406	CG1	VAL	A	52	26.064	49.202	-20.901	1.00	49.68 C
ATOM	407	CG2	VAL	A	52	27.029	48.555	-18.694	1.00	46.22 C
ATOM	408	N	VAL	A	53	23.491	46.999	-21.353	1.00	43.80 N
ATOM	409	CA	VAL	A	53	22.813	46.679	-22.584	1.00	51.71 C
ATOM	410	C	VAL	A	53	22.126	47.901	-23.192	1.00	60.49 C
ATOM	411	O	VAL	A	53	21.288	48.550	-22.564	1.00	55.82 O
ATOM	412	CB	VAL	A	53	21.770	45.573	-22.343	1.00	57.05 C
ATOM	413	CG1	VAL	A	53	20.897	45.392	-23.569	1.00	61.58 C
ATOM	414	CG2	VAL	A	53	22.478	44.269	-22.008	1.00	51.45 C
ATOM	415	N	TRP	A	54	22.511	48.205	-24.422	1.00	65.48 N
ATOM	416	CA	TRP	A	54	21.948	49.309	-25.178	1.00	74.11 C
ATOM	417	C	TRP	A	54	20.581	48.813	-25.650	1.00	74.48 C
ATOM	418	O	TRP	A	54	20.475	47.706	-26.167	1.00	72.95 O
ATOM	419	CB	TRP	A	54	22.851	49.571	-26.365	1.00	82.17 C
ATOM	420	CG	TRP	A	54	22.565	50.791	-27.135	1.00	99.79 C
ATOM	421	CD1	TRP	A	54	22.877	52.073	-26.787	1.00	102.50 C
ATOM	422	CD2	TRP	A	54	22.021	50.849	-28.456	1.00	107.53 C

Table 2

ATOM	423	NE1	TRP	A	54	22.573	52.929	-27.817	1.00	109.34 N
ATOM	424	CE2	TRP	A	54	22.045	52.205	-28.852	1.00	111.35 C
ATOM	425	CE3	TRP	A	54	21.515	49.889	-29.343	1.00	108.73 C
ATOM	426	CZ2	TRP	A	54	21.590	52.619	-30.108	1.00	112.86 C
ATOM	427	CZ3	TRP	A	54	21.061	50.305	-30.591	1.00	109.55 C
ATOM	428	CH2	TRP	A	54	21.100	51.662	-30.959	1.00	110.38 C
ATOM	429	N	ASN	A	55	19.537	49.612	-25.471	1.00	71.63 N
ATOM	430	CA	ASN	A	55	18.205	49.185	-25.878	1.00	76.76 C
ATOM	431	C	ASN	A	55	17.845	49.651	-27.281	1.00	81.91 C
ATOM	432	O	ASN	A	55	17.573	48.846	-28.168	1.00	88.33 O
ATOM	433	CB	ASN	A	55	17.197	49.689	-24.858	1.00	71.55 C
ATOM	434	CG	ASN	A	55	17.474	49.141	-23.476	1.00	75.04 C
ATOM	435	OD1	ASN	A	55	17.374	47.932	-23.246	1.00	72.25 O
ATOM	436	ND2	ASN	A	55	17.841	50.021	-22.550	1.00	50.95 N
ATOM	437	N	ASP	A	56	17.833	50.962	-27.455	1.00	88.42 N
ATOM	438	CA	ASP	A	56	17.548	51.607	-28.722	1.00	96.25 C
ATOM	439	C	ASP	A	56	18.566	52.727	-28.677	1.00	101.81 C
ATOM	440	O	ASP	A	56	19.369	52.797	-27.736	1.00	102.77 O
ATOM	441	CB	ASP	A	56	16.107	52.147	-28.744	1.00	95.48 C
ATOM	442	CG	ASP	A	56	15.707	52.811	-27.433	1.00	93.76 C
ATOM	443	OD1	ASP	A	56	16.451	53.704	-26.985	1.00	85.05 O
ATOM	444	OD2	ASP	A	56	14.658	52.452	-26.849	1.00	93.98 O
ATOM	445	N	ASP	A	57	18.599	53.607	-29.663	1.00	102.50 N
ATOM	446	CA	ASP	A	57	19.610	54.674	-29.562	1.00	102.11 C
ATOM	447	C	ASP	A	57	19.218	55.678	-28.491	1.00	97.41 C
ATOM	448	O	ASP	A	57	19.933	56.652	-28.258	1.00	97.40 O
ATOM	449	CB	ASP	A	57	19.781	55.395	-30.900	1.00	112.19 C
ATOM	450	CG	ASP	A	57	21.068	56.116	-30.995	1.00	121.70 C
ATOM	451	OD1	ASP	A	57	21.660	56.543	-29.959	1.00	128.34 O
ATOM	452	OD2	ASP	A	57	21.589	56.364	-32.125	1.00	123.94 O
ATOM	453	N	ASP	A	58	18.084	55.433	-27.843	1.00	90.49 N
ATOM	454	CA	ASP	A	58	17.622	56.352	-26.826	1.00	87.06 C
ATOM	455	C	ASP	A	58	18.071	55.997	-25.427	1.00	73.82 C
ATOM	456	O	ASP	A	58	18.180	56.880	-24.577	1.00	62.84 O
ATOM	457	CB	ASP	A	58	16.093	56.433	-26.809	1.00	103.58 C
ATOM	458	CG	ASP	A	58	15.487	56.564	-28.191	1.00	113.84 C
ATOM	459	OD1	ASP	A	58	15.498	57.677	-28.763	1.00	117.69 O
ATOM	460	OD2	ASP	A	58	14.997	55.534	-28.700	1.00	121.72 O
ATOM	461	N	SER	A	59	18.320	54.717	-25.174	1.00	64.75 N
ATOM	462	CA	SER	A	59	18.681	54.313	-23.828	1.00	61.90 C
ATOM	463	C	SER	A	59	19.628	53.131	-23.689	1.00	64.15 C
ATOM	464	O	SER	A	59	19.869	52.359	-24.627	1.00	60.43 O
ATOM	465	CB	SER	A	59	17.408	54.000	-23.052	1.00	55.02 C
ATOM	466	OG	SER	A	59	16.760	52.881	-23.625	1.00	62.54 O
ATOM	467	N	SER	A	60	20.145	53.005	-22.473	1.00	58.32 N
ATOM	468	CA	SER	A	60	21.062	51.941	-22.111	1.00	53.12 C
ATOM	469	C	SER	A	60	20.694	51.465	-20.708	1.00	51.38 C
ATOM	470	O	SER	A	60	20.439	52.271	-19.815	1.00	50.11 O
ATOM	471	CB	SER	A	60	22.502	52.451	-22.127	1.00	48.06 C
ATOM	472	OG	SER	A	60	23.407	51.420	-21.751	1.00	54.93 O
ATOM	473	N	THR	A	61	20.667	50.157	-20.509	1.00	41.41 N
ATOM	474	CA	THR	A	61	20.308	49.618	-19.206	1.00	44.19 C
ATOM	475	C	THR	A	61	21.489	48.979	-18.501	1.00	42.41 C
ATOM	476	O	THR	A	61	22.227	48.188	-19.081	1.00	46.93 O
ATOM	477	CB	THR	A	61	19.183	48.583	-19.353	1.00	47.49 C
ATOM	478	OG1	THR	A	61	18.023	49.233	-19.880	1.00	56.06 O
ATOM	479	CG2	THR	A	61	18.837	47.945	-18.004	1.00	45.18 C
ATOM	480	N	LEU	A	62	21.674	49.359	-17.247	1.00	37.61 N
ATOM	481	CA	LEU	A	62	22.731	48.797	-16.432	1.00	39.04 C

Table 2

ATOM	482	C	LEU	A	62	22.076	47.810	-15.475	1.00	38.19 C
ATOM	483	O	LEU	A	62	21.171	48.185	-14.722	1.00	38.43 O
ATOM	484	CB	LEU	A	62	23.431	49.896	-15.628	1.00	34.82 C
ATOM	485	CG	LEU	A	62	24.273	49.373	-14.461	1.00	46.86 C
ATOM	486	CD1	LEU	A	62	25.418	48.550	-14.996	1.00	41.11 C
ATOM	487	CD2	LEU	A	62	24.797	50.517	-13.617	1.00	40.98 C
ATOM	488	N	THR	A	63	22.488	46.548	-15.514	1.00	34.32 N
ATOM	489	CA	THR	A	63	21.930	45.570	-14.583	1.00	42.11 C
ATOM	490	C	THR	A	63	23.043	45.058	-13.694	1.00	38.02 C
ATOM	491	O	THR	A	63	24.086	44.634	-14.181	1.00	39.91 O
ATOM	492	CB	THR	A	63	21.312	44.333	-15.284	1.00	44.60 C
ATOM	493	OG1	THR	A	63	20.291	44.746	-16.193	1.00	38.13 O
ATOM	494	CG2	THR	A	63	20.709	43.388	-14.247	1.00	41.53 C
ATOM	495	N	ILE	A	64	22.831	45.096	-12.390	1.00	32.30 N
ATOM	496	CA	ILE	A	64	23.835	44.596	-11.464	1.00	40.27 C
ATOM	497	C	ILE	A	64	23.288	43.299	-10.884	1.00	44.61 C
ATOM	498	O	ILE	A	64	22.400	43.324	-10.032	1.00	43.38 O
ATOM	499	CB	ILE	A	64	24.116	45.600	-10.319	1.00	43.07 C
ATOM	500	CG1	ILE	A	64	24.757	46.868	-10.894	1.00	50.00 C
ATOM	501	CG2	ILE	A	64	25.032	44.962	-9.265	1.00	36.35 C
ATOM	502	CD1	ILE	A	64	25.080	47.930	-9.867	1.00	45.66 C
ATOM	503	N	TYR	A	65	23.811	42.175	-11.373	1.00	41.50 N
ATOM	504	CA	TYR	A	65	23.398	40.851	-10.917	1.00	41.75 C
ATOM	505	C	TYR	A	65	24.239	40.399	-9.746	1.00	46.17 C
ATOM	506	O	TYR	A	65	25.400	40.796	-9.628	1.00	46.44 O
ATOM	507	CB	TYR	A	65	23.591	39.814	-12.023	1.00	39.24 C
ATOM	508	CG	TYR	A	65	22.643	39.936	-13.177	1.00	46.02 C
ATOM	509	CD1	TYR	A	65	23.074	40.408	-14.415	1.00	43.20 C
ATOM	510	CD2	TYR	A	65	21.304	39.560	-13.035	1.00	40.19 C
ATOM	511	CE1	TYR	A	65	22.198	40.503	-15.492	1.00	46.92 C
ATOM	512	CE2	TYR	A	65	20.406	39.644	-14.117	1.00	42.02 C
ATOM	513	CZ	TYR	A	65	20.868	40.117	-15.337	1.00	47.29 C
ATOM	514	OH	TYR	A	65	20.008	40.185	-16.399	1.00	46.88 O
ATOM	515	N	ASN	A	66	23.660	39.556	-8.897	1.00	43.81 N
ATOM	516	CA	ASN	A	66	24.368	38.990	-7.756	1.00	48.17 C
ATOM	517	C	ASN	A	66	25.277	40.002	-7.062	1.00	48.24 C
ATOM	518	O	ASN	A	66	26.489	39.792	-6.955	1.00	48.04 O
ATOM	519	CB	ASN	A	66	25.206	37.817	-8.241	1.00	44.79 C
ATOM	520	CG	ASN	A	66	25.844	37.052	-7.100	1.00	58.80 C
ATOM	521	OD1	ASN	A	66	26.868	36.393	-7.279	1.00	62.64 O
ATOM	522	ND2	ASN	A	66	25.237	37.127	-5.919	1.00	60.17 N
ATOM	523	N	ALA	A	67	24.684	41.080	-6.566	1.00	47.68 N
ATOM	524	CA	ALA	A	67	25.448	42.151	-5.935	1.00	40.81 C
ATOM	525	C	ALA	A	67	26.301	41.798	-4.739	1.00	49.08 C
ATOM	526	O	ALA	A	67	25.937	40.963	-3.910	1.00	47.57 O
ATOM	527	CB	ALA	A	67	24.523	43.290	-5.553	1.00	44.48 C
ATOM	528	N	ASN	A	68	27.435	42.482	-4.649	1.00	50.95 N
ATOM	529	CA	ASN	A	68	28.344	42.315	-3.529	1.00	54.43 C
ATOM	530	C	ASN	A	68	28.763	43.719	-3.093	1.00	55.80 C
ATOM	531	O	ASN	A	68	28.665	44.678	-3.872	1.00	45.45 O
ATOM	532	CB	ASN	A	68	29.557	41.476	-3.922	1.00	51.73 C
ATOM	533	CG	ASN	A	68	30.494	42.201	-4.854	1.00	61.49 C
ATOM	534	OD1	ASN	A	68	30.920	43.322	-4.579	1.00	60.88 O
ATOM	535	ND2	ASN	A	68	30.835	41.554	-5.963	1.00	52.62 N
ATOM	536	N	ILE	A	69	29.235	43.835	-1.856	1.00	52.73 N
ATOM	537	CA	ILE	A	69	29.630	45.118	-1.285	1.00	58.71 C
ATOM	538	C	ILE	A	69	30.545	45.990	-2.137	1.00	51.79 C
ATOM	539	O	ILE	A	69	30.483	47.208	-2.043	1.00	52.79 O
ATOM	540	CB	ILE	A	69	30.299	44.937	0.095	1.00	60.50 C

Table 2

ATOM	541	CG1	ILE	A	69	31.681	44.301	-0.063	1.00	67.17	C
ATOM	542	CG2	ILE	A	69	29.410	44.091	0.987	1.00	59.59	C
ATOM	543	CD1	ILE	A	69	32.506	44.314	1.211	1.00	80.29	C
ATOM	544	N	ASP	A	70	31.396	45.384	-2.956	1.00	46.36	N
ATOM	545	CA	ASP	A	70	32.277	46.184	-3.781	1.00	50.45	C
ATOM	546	C	ASP	A	70	31.587	46.792	-4.991	1.00	58.77	C
ATOM	547	O	ASP	A	70	32.227	47.477	-5.784	1.00	53.61	O
ATOM	548	CB	ASP	A	70	33.473	45.369	-4.241	1.00	50.41	C
ATOM	549	CG	ASP	A	70	34.388	44.991	-3.088	1.00	69.82	C
ATOM	550	OD1	ASP	A	70	34.622	45.851	-2.208	1.00	68.65	O
ATOM	551	OD2	ASP	A	70	34.878	43.842	-3.064	1.00	67.67	O
ATOM	552	N	ASP	A	71	30.290	46.540	-5.144	1.00	54.09	N
ATOM	553	CA	ASP	A	71	29.554	47.102	-6.269	1.00	50.10	C
ATOM	554	C	ASP	A	71	28.969	48.474	-5.898	1.00	52.41	C
ATOM	555	O	ASP	A	71	28.508	49.224	-6.764	1.00	47.41	O
ATOM	556	CB	ASP	A	71	28.406	46.166	-6.708	1.00	49.99	C
ATOM	557	CG	ASP	A	71	28.892	44.834	-7.302	1.00	49.02	C
ATOM	558	OD1	ASP	A	71	29.813	44.835	-8.146	1.00	46.46	O
ATOM	559	OD2	ASP	A	71	28.324	43.784	-6.929	1.00	50.74	O
ATOM	560	N	ALA	A	72	28.987	48.601	-4.610	1.00	42.72	N
ATOM	561	CA	ALA	A	72	28.429	50.063	-4.133	1.00	45.31	C
ATOM	562	C	ALA	A	72	29.129	51.291	-4.686	1.00	47.73	C
ATOM	563	O	ALA	A	72	30.326	51.268	-4.977	1.00	47.41	O
ATOM	564	CB	ALA	A	72	28.460	50.107	-2.604	1.00	47.05	C
ATOM	565	N	GLY	A	73	28.378	52.374	-4.821	1.00	48.72	N
ATOM	566	CA	GLY	A	73	28.976	53.593	-5.322	1.00	54.09	C
ATOM	567	C	GLY	A	73	28.144	54.331	-6.341	1.00	51.98	C
ATOM	568	O	GLY	A	73	27.018	53.939	-6.653	1.00	49.57	O
ATOM	569	N	ILE	A	74	28.716	55.413	-6.859	1.00	51.79	N
ATOM	570	CA	ILE	A	74	28.052	56.242	-7.850	1.00	48.58	C
ATOM	571	C	ILE	A	74	28.428	55.760	-9.237	1.00	47.75	C
ATOM	572	O	ILE	A	74	29.603	55.780	-9.620	1.00	46.87	O
ATOM	573	CB	ILE	A	74	28.475	57.717	-7.705	1.00	54.10	C
ATOM	574	CG1	ILE	A	74	28.061	58.227	-6.323	1.00	60.29	C
ATOM	575	CG2	ILE	A	74	27.860	58.551	-8.816	1.00	51.72	C
ATOM	576	CD1	ILE	A	74	28.463	59.656	-6.041	1.00	55.15	C
ATOM	577	N	TYR	A	75	27.429	55.272	-9.960	1.00	39.87	N
ATOM	578	CA	TYR	A	75	27.637	54.826	-11.330	1.00	48.23	C
ATOM	579	C	TYR	A	75	27.168	56.010	-12.126	1.00	48.15	C
ATOM	580	O	TYR	A	75	26.293	56.764	-11.682	1.00	46.43	O
ATOM	581	CB	TYR	A	75	26.745	53.629	-11.707	1.00	44.56	C
ATOM	582	CG	TYR	A	75	27.137	52.331	-11.050	1.00	47.56	C
ATOM	583	CD1	TYR	A	75	26.925	52.133	-9.682	1.00	39.03	C
ATOM	584	CD2	TYR	A	75	27.789	51.326	-11.773	1.00	43.44	C
ATOM	585	CE1	TYR	A	75	27.356	50.967	-9.045	1.00	39.99	C
ATOM	586	CE2	TYR	A	75	28.230	50.162	-11.146	1.00	32.79	C
ATOM	587	CZ	TYR	A	75	28.010	49.990	-9.778	1.00	35.84	C
ATOM	588	OH	TYR	A	75	28.463	48.851	-9.153	1.00	43.95	O
ATOM	589	N	LYS	A	76	27.739	56.201	-13.299	1.00	48.85	N
ATOM	590	CA	LYS	A	76	27.270	57.305	-14.090	1.00	48.84	C
ATOM	591	C	LYS	A	76	27.178	56.938	-15.532	1.00	44.98	C
ATOM	592	O	LYS	A	76	27.912	56.092	-16.052	1.00	47.18	O
ATOM	593	CB	LYS	A	76	28.115	58.551	-13.857	1.00	56.56	C
ATOM	594	CG	LYS	A	76	29.442	58.619	-14.520	1.00	59.09	C
ATOM	595	CD	LYS	A	76	30.046	59.941	-14.072	1.00	66.83	C
ATOM	596	CE	LYS	A	76	31.142	60.452	-14.968	1.00	71.43	C
ATOM	597	NZ	LYS	A	76	31.553	61.794	-14.449	1.00	73.15	N
ATOM	598	N	CYS	A	77	26.194	57.553	-16.153	1.00	45.89	N
ATOM	599	CA	CYS	A	77	25.888	57.319	-17.532	1.00	44.65	C

ATOM	600	C	CYS	A	77	26.233	58.600	-18.270	1.00	47.89 C
ATOM	601	O	CYS	A	77	25.718	59.666	-17.945	1.00	52.98 O
ATOM	602	CB	CYS	A	77	24.401	57.004	-17.652	1.00	42.61 C
ATOM	603	SG	CYS	A	77	23.808	56.802	-19.350	1.00	61.23 S
ATOM	604	N	VAL	A	78	27.122	58.494	-19.249	1.00	50.12 N
ATOM	605	CA	VAL	A	78	27.547	59.658	-20.019	1.00	46.50 C
ATOM	606	C	VAL	A	78	27.082	59.581	-21.471	1.00	43.99 C
ATOM	607	O	VAL	A	78	27.222	58.552	-22.131	1.00	48.45 O
ATOM	608	CB	VAL	A	78	29.084	59.795	-19.993	1.00	46.58 C
ATOM	609	CG1	VAL	A	78	29.517	61.010	-20.820	1.00	51.99 C
ATOM	610	CG2	VAL	A	78	29.566	59.942	-18.547	1.00	41.06 C
ATOM	611	N	VAL	A	79	26.521	60.672	-21.965	1.00	48.68 N
ATOM	612	CA	VAL	A	79	26.047	60.720	-23.343	1.00	57.39 C
ATOM	613	C	VAL	A	79	26.945	61.666	-24.119	1.00	54.87 C
ATOM	614	O	VAL	A	79	27.194	62.792	-23.691	1.00	52.91 O
ATOM	615	CB	VAL	A	79	24.598	61.227	-23.417	1.00	60.20 C
ATOM	616	CG1	VAL	A	79	24.085	61.155	-24.848	1.00	54.06 C
ATOM	617	CG2	VAL	A	79	23.730	60.395	-22.487	1.00	56.02 C
ATOM	618	N	THR	A	80	27.452	61.191	-25.247	1.00	48.32 N
ATOM	619	CA	THR	A	80	28.313	62.011	-26.066	1.00	52.81 C
ATOM	620	C	THR	A	80	27.706	62.226	-27.450	1.00	54.17 C
ATOM	621	O	THR	A	80	27.501	61.266	-28.187	1.00	49.22 O
ATOM	622	CB	THR	A	80	29.691	61.371	-26.241	1.00	54.94 C
ATOM	623	OG1	THR	A	80	30.268	61.104	-24.954	1.00	54.31 O
ATOM	624	CG2	THR	A	80	30.601	62.318	-27.012	1.00	41.33 C
ATOM	625	N	ALA	A	81	27.430	63.487	-27.787	1.00	56.76 N
ATOM	626	CA	ALA	A	81	26.859	63.866	-29.088	1.00	58.85 C
ATOM	627	C	ALA	A	81	27.942	63.828	-30.165	1.00	58.97 C
ATOM	628	O	ALA	A	81	29.131	63.922	-29.847	1.00	53.72 O
ATOM	629	CB	ALA	A	81	26.263	65.265	-29.005	1.00	60.88 C
ATOM	630	N	GLU	A	82	27.528	63.712	-31.429	1.00	67.86 N
ATOM	631	CA	GLU	A	82	28.462	63.639	-32.555	1.00	73.18 C
ATOM	632	C	GLU	A	82	29.599	64.664	-32.507	1.00	68.06 C
ATOM	633	O	GLU	A	82	30.700	64.398	-32.993	1.00	65.36 O
ATOM	634	CB	GLU	A	82	27.707	63.768	-33.887	1.00	74.95 C
ATOM	635	CG	GLU	A	82	28.027	62.638	-34.868	1.00	98.35 C
ATOM	636	CD	GLU	A	82	27.295	62.768	-36.194	1.00	111.66 C
ATOM	637	OE1	GLU	A	82	26.071	63.034	-36.178	1.00	118.11 O
ATOM	638	OE2	GLU	A	82	27.942	62.594	-37.253	1.00	117.01 O
ATOM	639	N	ASP	A	83	29.340	65.821	-31.907	1.00	62.35 N
ATOM	640	CA	ASP	A	83	30.340	66.877	-31.812	1.00	67.89 C
ATOM	641	C	ASP	A	83	31.171	66.830	-30.533	1.00	71.00 C
ATOM	642	O	ASP	A	83	31.929	67.759	-30.246	1.00	73.73 O
ATOM	643	CB	ASP	A	83	29.653	68.230	-31.924	1.00	74.31 C
ATOM	644	CG	ASP	A	83	28.664	68.461	-30.815	1.00	82.18 C
ATOM	645	OD1	ASP	A	83	27.939	67.508	-30.462	1.00	93.75 O
ATOM	646	OD2	ASP	A	83	28.606	69.593	-30.301	1.00	87.77 O
ATOM	647	N	GLY	A	84	31.017	65.760	-29.759	1.00	69.26 N
ATOM	648	CA	GLY	A	84	31.790	65.617	-28.533	1.00	61.95 C
ATOM	649	C	GLY	A	84	31.242	66.254	-27.266	1.00	62.86 C
ATOM	650	O	GLY	A	84	31.851	66.139	-26.197	1.00	65.82 O
ATOM	651	N	THR	A	85	30.106	66.936	-27.361	1.00	55.77 N
ATOM	652	CA	THR	A	85	29.535	67.559	-26.176	1.00	63.65 C
ATOM	653	C	THR	A	85	28.929	66.445	-25.320	1.00	61.95 C
ATOM	654	O	THR	A	85	28.291	65.528	-25.839	1.00	56.86 O
ATOM	655	CB	THR	A	85	28.471	68.614	-26.555	1.00	61.72 C
ATOM	656	OG1	THR	A	85	27.458	68.019	-27.373	1.00	73.83 O
ATOM	657	CG2	THR	A	85	29.125	69.749	-27.325	1.00	69.89 C
ATOM	658	N	GLN	A	86	29.130	66.520	-24.011	1.00	58.16 N

Table 2

ATOM	659	CA	GLN	A	86	28.628	65.464	-23.141	1.00	63.76	C
ATOM	660	C	GLN	A	86	27.696	65.900	-22.030	1.00	62.47	C
ATOM	661	O	GLN	A	86	27.803	67.011	-21.505	1.00	64.92	O
ATOM	662	CB	GLN	A	86	29.793	64.715	-22.498	1.00	56.96	C
ATOM	663	CG	GLN	A	86	30.860	64.242	-23.460	1.00	50.20	C
ATOM	664	CD	GLN	A	86	31.964	63.519	-22.724	1.00	54.10	C
ATOM	665	OE1	GLN	A	86	32.390	63.965	-21.663	1.00	54.08	O
ATOM	666	NE2	GLN	A	86	32.436	62.401	-23.276	1.00	56.27	N
ATOM	667	N	SER	A	87	26.800	64.986	-21.667	1.00	63.47	N
ATOM	668	CA	SER	A	87	25.836	65.182	-20.588	1.00	68.11	C
ATOM	669	C	SER	A	87	25.889	63.906	-19.749	1.00	65.62	C
ATOM	670	O	SER	A	87	26.194	62.829	-20.270	1.00	69.37	O
ATOM	671	CB	SER	A	87	24.420	65.362	-21.150	1.00	75.52	C
ATOM	672	OG	SER	A	87	24.344	66.449	-22.057	1.00	88.36	O
ATOM	673	N	GLU	A	88	25.592	64.009	-18.460	1.00	63.19	N
ATOM	674	CA	GLU	A	88	25.623	62.827	-17.607	1.00	53.44	C
ATOM	675	C	GLU	A	88	24.532	62.803	-16.556	1.00	59.13	C
ATOM	676	O	GLU	A	88	23.942	63.824	-16.209	1.00	58.88	O
ATOM	677	CB	GLU	A	88	26.976	62.711	-16.904	1.00	60.59	C
ATOM	678	CG	GLU	A	88	27.272	63.816	-15.898	1.00	67.25	C
ATOM	679	CD	GLU	A	88	28.656	63.687	-15.277	1.00	78.40	C
ATOM	680	OE1	GLU	A	88	29.631	63.494	-16.035	1.00	79.36	O
ATOM	681	OE2	GLU	A	88	28.773	63.782	-14.033	1.00	81.96	O
ATOM	682	N	ALA	A	89	24.254	61.602	-16.079	1.00	54.88	N
ATOM	683	CA	ALA	A	89	23.283	61.384	-15.027	1.00	45.50	C
ATOM	684	C	ALA	A	89	24.036	60.407	-14.149	1.00	52.74	C
ATOM	685	O	ALA	A	89	24.777	59.552	-14.659	1.00	48.26	O
ATOM	686	CB	ALA	A	89	22.022	60.736	-15.567	1.00	53.66	C
ATOM	687	N	THR	A	90	23.887	60.549	-12.839	1.00	46.21	N
ATOM	688	CA	THR	A	90	24.558	59.647	-11.932	1.00	49.08	C
ATOM	689	C	THR	A	90	23.515	58.993	-11.051	1.00	49.13	C
ATOM	690	O	THR	A	90	22.402	59.516	-10.861	1.00	49.24	O
ATOM	691	CB	THR	A	90	25.587	60.376	-11.052	1.00	48.30	C
ATOM	692	OG1	THR	A	90	24.932	61.366	-10.256	1.00	53.97	O
ATOM	693	CG2	THR	A	90	26.640	61.041	-11.915	1.00	52.65	C
ATOM	694	N	VAL	A	91	23.871	57.823	-10.539	1.00	45.14	N
ATOM	695	CA	VAL	A	91	22.966	57.102	-9.667	1.00	48.65	C
ATOM	696	C	VAL	A	91	23.736	56.474	-8.527	1.00	45.53	C
ATOM	697	O	VAL	A	91	24.708	55.754	-8.740	1.00	47.93	O
ATOM	698	CB	VAL	A	91	22.164	56.035	-10.433	1.00	50.62	C
ATOM	699	CG1	VAL	A	91	23.113	55.013	-11.094	1.00	48.35	C
ATOM	700	CG2	VAL	A	91	21.177	55.349	-9.474	1.00	54.01	C
ATOM	701	N	ASN	A	92	23.304	56.773	-7.306	1.00	49.96	N
ATOM	702	CA	ASN	A	92	23.964	56.255	-6.116	1.00	50.90	C
ATOM	703	C	ASN	A	92	23.399	54.887	-5.780	1.00	45.05	C
ATOM	704	O	ASN	A	92	22.220	54.742	-5.466	1.00	48.81	O
ATOM	705	CB	ASN	A	92	23.757	57.200	-4.932	1.00	47.93	C
ATOM	706	CG	ASN	A	92	24.569	56.786	-3.724	1.00	54.25	C
ATOM	707	OD1	ASN	A	92	24.115	56.897	-2.584	1.00	56.44	O
ATOM	708	ND2	ASN	A	92	25.784	56.304	-3.969	1.00	54.09	N
ATOM	709	N	VAL	A	93	24.256	53.881	-5.851	1.00	46.44	N
ATOM	710	CA	VAL	A	93	23.831	52.527	-5.574	1.00	47.68	C
ATOM	711	C	VAL	A	93	24.387	52.085	-4.232	1.00	46.87	C
ATOM	712	O	VAL	A	93	25.602	52.009	-4.053	1.00	45.39	O
ATOM	713	CB	VAL	A	93	24.310	51.548	-6.679	1.00	44.88	C
ATOM	714	CG1	VAL	A	93	23.834	50.143	-6.365	1.00	50.34	C
ATOM	715	CG2	VAL	A	93	23.769	51.981	-8.042	1.00	51.13	C
ATOM	716	N	LYS	A	94	23.490	51.807	-3.290	1.00	52.11	N
ATOM	717	CA	LYS	A	94	23.902	51.347	-1.961	1.00	59.43	C

ATOM	718	C	LYS	A	94	23.774	49.832	-1.886	1.00	55.63 C
ATOM	719	O	LYS	A	94	22.871	49.241	-2.471	1.00	43.24 O
ATOM	720	CB	LYS	A	94	23.033	51.960	-0.855	1.00	55.35 C
ATOM	721	CG	LYS	A	94	23.173	53.464	-0.668	1.00	65.17 C
ATOM	722	CD	LYS	A	94	22.156	53.977	0.356	1.00	67.48 C
ATOM	723	CE	LYS	A	94	22.081	55.492	0.362	1.00	74.84 C
ATOM	724	NZ	LYS	A	94	21.040	55.986	1.310	1.00	78.54 N
ATOM	725	N	ILE	A	95	24.699	49.202	-1.181	1.00	56.66 N
ATOM	726	CA	ILE	A	95	24.658	47.762	-1.004	1.00	56.71 C
ATOM	727	C	ILE	A	95	24.467	47.546	0.495	1.00	59.65 C
ATOM	728	O	ILE	A	95	25.004	48.298	1.305	1.00	53.96 O
ATOM	729	CB	ILE	A	95	25.981	47.086	-1.451	1.00	50.11 C
ATOM	730	CG1	ILE	A	95	26.247	47.361	-2.935	1.00	58.21 C
ATOM	731	CG2	ILE	A	95	25.905	45.584	-1.206	1.00	55.81 C
ATOM	732	CD1	ILE	A	95	25.141	46.878	-3.869	1.00	46.59 C
ATOM	733	N	PHE	A	96	23.670	46.553	0.863	1.00	56.77 N
ATOM	734	CA	PHE	A	96	23.464	46.249	2.269	1.00	56.57 C
ATOM	735	C	PHE	A	96	23.070	44.791	2.380	1.00	52.33 C
ATOM	736	O	PHE	A	96	22.921	44.087	1.375	1.00	55.58 O
ATOM	737	CB	PHE	A	96	22.389	47.146	2.893	1.00	51.68 C
ATOM	738	CG	PHE	A	96	20.984	46.731	2.570	1.00	55.80 C
ATOM	739	CD1	PHE	A	96	20.078	46.441	3.589	1.00	56.18 C
ATOM	740	CD2	PHE	A	96	20.565	46.630	1.249	1.00	53.68 C
ATOM	741	CE1	PHE	A	96	18.770	46.055	3.287	1.00	61.36 C
ATOM	742	CE2	PHE	A	96	19.268	46.249	0.932	1.00	54.41 C
ATOM	743	CZ	PHE	A	96	18.362	45.959	1.951	1.00	51.56 C
ATOM	744	N	GLN	A	97	22.929	44.323	3.607	1.00	44.80 N
ATOM	745	CA	GLN	A	97	22.565	42.945	3.819	1.00	41.35 C
ATOM	746	C	GLN	A	97	21.257	42.956	4.559	1.00	43.49 C
ATOM	747	O	GLN	A	97	21.185	43.352	5.725	1.00	48.61 O
ATOM	748	CB	GLN	A	97	23.639	42.220	4.639	1.00	50.03 C
ATOM	749	CG	GLN	A	97	23.239	40.811	5.074	1.00	42.38 C
ATOM	750	CD	GLN	A	97	22.968	39.885	3.899	1.00	45.87 C
ATOM	751	OE1	GLN	A	97	23.879	39.539	3.148	1.00	50.97 O
ATOM	752	NE2	GLN	A	97	21.712	39.485	3.725	1.00	43.50 N
ATOM	753	N	LYS	A	98	20.208	42.557	3.861	1.00	43.56 N
ATOM	754	CA	LYS	A	98	18.914	42.503	4.493	1.00	50.07 C
ATOM	755	C	LYS	A	98	18.988	41.436	5.594	1.00	45.12 C
ATOM	756	O	LYS	A	98	19.772	40.483	5.518	1.00	44.19 O
ATOM	757	CB	LYS	A	98	17.835	42.141	3.467	1.00	42.89 C
ATOM	758	CG	LYS	A	98	17.806	40.689	3.029	1.00	54.06 C
ATOM	759	CD	LYS	A	98	16.620	40.432	2.091	1.00	70.03 C
ATOM	760	CE	LYS	A	98	16.542	38.972	1.674	1.00	74.47 C
ATOM	761	NZ	LYS	A	98	15.366	38.722	0.799	1.00	87.06 N
ATOM	762	N	LEU	A	99	18.187	41.633	6.625	1.00	42.33 N
ATOM	763	CA	LEU	A	99	18.112	40.718	7.743	1.00	48.11 C
ATOM	764	C	LEU	A	99	17.731	39.322	7.271	1.00	51.43 C
ATOM	765	O	LEU	A	99	16.622	39.119	6.784	1.00	54.69 O
ATOM	766	CB	LEU	A	99	17.058	41.223	8.727	1.00	40.97 C
ATOM	767	CG	LEU	A	99	16.874	40.365	9.974	1.00	51.52 C
ATOM	768	CD1	LEU	A	99	18.114	40.494	10.829	1.00	49.68 C
ATOM	769	CD2	LEU	A	99	15.663	40.822	10.765	1.00	51.15 C
ATOM	770	N	MET	A	100	18.643	38.358	7.388	1.00	48.12 N
ATOM	771	CA	MET	A	100	18.321	36.984	6.995	1.00	51.56 C
ATOM	772	C	MET	A	100	19.033	35.977	7.907	1.00	51.77 C
ATOM	773	O	MET	A	100	19.991	36.322	8.621	1.00	39.76 O
ATOM	774	CB	MET	A	100	18.650	36.727	5.512	1.00	61.21 C
ATOM	775	CG	MET	A	100	20.116	36.564	5.166	1.00	69.49 C
ATOM	776	SD	MET	A	100	20.416	36.505	3.372	1.00	84.60 S

ATOM	777	CE	MET	A	100	19.818	34.884	2.949	1.00	92.44 C
ATOM	778	N	PHE	A	101	18.531	34.745	7.908	1.00	45.49 N
ATOM	779	CA	PHE	A	101	19.085	33.684	8.732	1.00	50.26 C
ATOM	780	C	PHE	A	101	20.138	32.893	7.995	1.00	43.40 C
ATOM	781	O	PHE	A	101	19.907	32.400	6.902	1.00	61.65 O
ATOM	782	CB	PHE	A	101	17.969	32.769	9.210	1.00	46.80 C
ATOM	783	CG	PHE	A	101	17.019	33.450	10.137	1.00	46.54 C
ATOM	784	CD1	PHE	A	101	15.900	34.112	9.652	1.00	52.32 C
ATOM	785	CD2	PHE	A	101	17.274	33.488	11.499	1.00	44.46 C
ATOM	786	CE1	PHE	A	101	15.054	34.822	10.516	1.00	43.20 C
ATOM	787	CE2	PHE	A	101	16.441	34.192	12.366	1.00	48.20 C
ATOM	788	CZ	PHE	A	101	15.322	34.858	11.869	1.00	48.40 C
ATOM	789	N	LYS	A	102	21.302	32.771	8.611	1.00	51.46 N
ATOM	790	CA	LYS	A	102	22.420	32.066	8.009	1.00	48.23 C
ATOM	791	C	LYS	A	102	22.516	30.619	8.468	1.00	54.86 C
ATOM	792	O	LYS	A	102	22.768	29.712	7.668	1.00	62.07 O
ATOM	793	CB	LYS	A	102	23.714	32.799	8.340	1.00	57.97 C
ATOM	794	CG	LYS	A	102	24.954	32.199	7.720	1.00	71.82 C
ATOM	795	CD	LYS	A	102	26.170	33.021	8.108	1.00	82.19 C
ATOM	796	CE	LYS	A	102	27.335	32.773	7.169	1.00	88.42 C
ATOM	797	NZ	LYS	A	102	28.516	33.602	7.540	1.00	98.10 N
ATOM	798	N	ASN	A	103	22.328	30.409	9.763	1.00	47.83 N
ATOM	799	CA	ASN	A	103	22.379	29.081	10.339	1.00	43.78 C
ATOM	800	C	ASN	A	103	21.419	29.084	11.525	1.00	45.04 C
ATOM	801	O	ASN	A	103	21.661	29.751	12.534	1.00	40.24 O
ATOM	802	CB	ASN	A	103	23.802	28.764	10.800	1.00	45.29 C
ATOM	803	CG	ASN	A	103	23.886	27.468	11.565	1.00	46.73 C
ATOM	804	OD1	ASN	A	103	23.582	26.402	11.037	1.00	54.61 O
ATOM	805	ND2	ASN	A	103	24.308	27.552	12.822	1.00	50.10 N
ATOM	806	N	ALA	A	104	20.312	28.369	11.379	1.00	40.89 N
ATOM	807	CA	ALA	A	104	19.304	28.264	12.422	1.00	48.41 C
ATOM	808	C	ALA	A	104	18.651	26.906	12.200	1.00	52.07 C
ATOM	809	O	ALA	A	104	17.490	26.811	11.829	1.00	51.94 O
ATOM	810	CB	ALA	A	104	18.280	29.359	12.241	1.00	53.18 C
ATOM	811	N	PRO	A	105	19.386	25.834	12.461	1.00	47.52 N
ATOM	812	CA	PRO	A	105	18.873	24.481	12.265	1.00	45.57 C
ATOM	813	C	PRO	A	105	17.700	24.096	13.112	1.00	47.49 C
ATOM	814	O	PRO	A	105	17.508	24.606	14.223	1.00	41.72 O
ATOM	815	CB	PRO	A	105	20.087	23.588	12.501	1.00	49.47 C
ATOM	816	CG	PRO	A	105	21.055	24.460	13.270	1.00	52.18 C
ATOM	817	CD	PRO	A	105	20.631	25.867	13.230	1.00	52.90 C
ATOM	818	N	THR	A	106	16.864	23.260	12.515	1.00	48.69 N
ATOM	819	CA	THR	A	106	15.717	22.758	13.215	1.00	52.32 C
ATOM	820	C	THR	A	106	15.529	21.322	12.759	1.00	58.90 C
ATOM	821	O	THR	A	106	15.672	20.999	11.581	1.00	55.09 O
ATOM	822	CB	THR	A	106	14.447	23.612	12.955	1.00	53.67 C
ATOM	823	OG1	THR	A	106	13.355	23.053	13.698	1.00	54.59 O
ATOM	824	CG2	THR	A	106	14.097	23.641	11.468	1.00	58.16 C
ATOM	825	N	PRO	A	107	15.275	20.424	13.714	1.00	52.16 N
ATOM	826	CA	PRO	A	107	15.184	20.737	15.138	1.00	43.22 C
ATOM	827	C	PRO	A	107	16.585	20.810	15.732	1.00	47.05 C
ATOM	828	O	PRO	A	107	17.578	20.532	15.064	1.00	45.59 O
ATOM	829	CB	PRO	A	107	14.426	19.539	15.688	1.00	49.39 C
ATOM	830	CG	PRO	A	107	15.052	18.411	14.902	1.00	55.45 C
ATOM	831	CD	PRO	A	107	15.065	18.986	13.480	1.00	55.64 C
ATOM	832	N	GLN	A	108	16.650	21.202	16.994	1.00	40.58 N
ATOM	833	CA	GLN	A	108	17.901	21.229	17.709	1.00	46.97 C
ATOM	834	C	GLN	A	108	17.566	20.339	18.896	1.00	44.47 C
ATOM	835	O	GLN	A	108	16.492	20.467	19.489	1.00	36.69 O

ATOM	836	CB	GLN	A	108	18.271	22.657	18.084	1.00	40.68	C
ATOM	837	CG	GLN	A	108	18.770	23.436	16.846	1.00	37.05	C
ATOM	838	CD	GLN	A	108	19.203	24.847	17.171	1.00	40.43	C
ATOM	839	OE1	GLN	A	108	19.879	25.073	18.172	1.00	36.29	O
ATOM	840	NE2	GLN	A	108	18.828	25.805	16.332	1.00	37.82	N
ATOM	841	N	GLU	A	109	18.469	19.413	19.203	1.00	38.32	N
ATOM	842	CA	GLU	A	109	18.261	18.425	20.257	1.00	39.59	C
ATOM	843	C	GLU	A	109	19.216	18.551	21.424	1.00	44.20	C
ATOM	844	O	GLU	A	109	20.380	18.922	21.254	1.00	41.88	O
ATOM	845	CB	GLU	A	109	18.364	17.033	19.637	1.00	39.87	C
ATOM	846	CG	GLU	A	109	17.437	16.885	18.448	1.00	45.54	C
ATOM	847	CD	GLU	A	109	17.358	15.478	17.912	1.00	49.95	C
ATOM	848	OE1	GLU	A	109	17.335	14.518	18.713	1.00	54.48	O
ATOM	849	OE2	GLU	A	109	17.295	15.330	16.678	1.00	54.37	O
ATOM	850	N	PHE	A	110	18.713	18.223	22.609	1.00	36.31	N
ATOM	851	CA	PHE	A	110	19.491	18.314	23.825	1.00	37.31	C
ATOM	852	C	PHE	A	110	19.154	17.167	24.748	1.00	44.15	C
ATOM	853	O	PHE	A	110	18.071	16.596	24.694	1.00	42.74	O
ATOM	854	CB	PHE	A	110	19.202	19.643	24.531	1.00	29.73	C
ATOM	855	CG	PHE	A	110	19.299	20.831	23.612	1.00	36.45	C
ATOM	856	CD1	PHE	A	110	18.189	21.286	22.922	1.00	37.59	C
ATOM	857	CD2	PHE	A	110	20.522	21.445	23.387	1.00	35.71	C
ATOM	858	CE1	PHE	A	110	18.301	22.337	22.006	1.00	49.86	C
ATOM	859	CE2	PHE	A	110	20.649	22.489	22.476	1.00	43.61	C
ATOM	860	CZ	PHE	A	110	19.533	22.939	21.785	1.00	39.36	C
ATOM	861	N	LYS	A	111	20.108	16.819	25.592	1.00	38.44	N
ATOM	862	CA	LYS	A	111	19.909	15.745	26.533	1.00	39.53	C
ATOM	863	C	LYS	A	111	19.327	16.395	27.769	1.00	33.66	C
ATOM	864	O	LYS	A	111	19.832	17.419	28.238	1.00	37.40	O
ATOM	865	CB	LYS	A	111	21.254	15.075	26.845	1.00	35.52	C
ATOM	866	CG	LYS	A	111	21.185	13.974	27.890	1.00	45.41	C
ATOM	867	CD	LYS	A	111	22.548	13.272	28.006	1.00	51.44	C
ATOM	868	CE	LYS	A	111	22.515	12.114	29.000	1.00	58.54	C
ATOM	869	NZ	LYS	A	111	23.657	11.172	28.765	1.00	62.26	N
ATOM	870	N	GLU	A	112	18.255	15.810	28.287	1.00	39.60	N
ATOM	871	CA	GLU	A	112	17.614	16.339	29.478	1.00	42.51	C
ATOM	872	C	GLU	A	112	18.627	16.706	30.569	1.00	37.78	C
ATOM	873	O	GLU	A	112	19.554	15.950	30.846	1.00	41.69	O
ATOM	874	CB	GLU	A	112	16.621	15.312	30.034	1.00	42.05	C
ATOM	875	CG	GLU	A	112	15.743	15.888	31.120	1.00	48.02	C
ATOM	876	CD	GLU	A	112	14.735	14.886	31.675	1.00	67.88	C
ATOM	877	OE1	GLU	A	112	13.582	15.304	31.937	1.00	64.90	O
ATOM	878	OE2	GLU	A	112	15.093	13.700	31.865	1.00	70.27	O
ATOM	879	N	GLY	A	113	18.448	17.875	31.175	1.00	41.71	N
ATOM	880	CA	GLY	A	113	19.350	18.298	32.228	1.00	43.96	C
ATOM	881	C	GLY	A	113	20.555	19.128	31.824	1.00	46.88	C
ATOM	882	O	GLY	A	113	21.087	19.877	32.652	1.00	44.90	O
ATOM	883	N	GLU	A	114	21.017	19.021	30.584	1.00	41.27	N
ATOM	884	CA	GLU	A	114	22.181	19.830	30.227	1.00	49.33	C
ATOM	885	C	GLU	A	114	21.739	21.260	29.927	1.00	46.85	C
ATOM	886	O	GLU	A	114	20.539	21.551	29.864	1.00	45.47	O
ATOM	887	CB	GLU	A	114	22.957	19.199	29.052	1.00	46.70	C
ATOM	888	CG	GLU	A	114	22.319	19.293	27.682	1.00	49.46	C
ATOM	889	CD	GLU	A	114	23.076	18.490	26.613	1.00	56.05	C
ATOM	890	OE1	GLU	A	114	24.174	17.946	26.894	1.00	59.22	O
ATOM	891	OE2	GLU	A	114	22.565	18.407	25.482	1.00	51.60	O
ATOM	892	N	ASP	A	115	22.689	22.181	29.822	1.00	42.06	N
ATOM	893	CA	ASP	A	115	22.323	23.554	29.512	1.00	46.33	C
ATOM	894	C	ASP	A	115	22.184	23.568	28.018	1.00	46.24	C

ATOM	895	O	ASP	A	115	23.107	23.195	27.299	1.00	51.16 O
ATOM	896	CB	ASP	A	115	23.394	24.525	29.976	1.00	52.16 C
ATOM	897	CG	ASP	A	115	23.530	24.535	31.475	1.00	58.98 C
ATOM	898	OD1	ASP	A	115	22.515	24.291	32.169	1.00	56.34 O
ATOM	899	OD2	ASP	A	115	24.647	24.785	31.959	1.00	74.61 O
ATOM	900	N	ALA	A	116	21.009	23.943	27.536	1.00	40.21 N
ATOM	901	CA	ALA	A	116	20.812	23.937	26.105	1.00	41.98 C
ATOM	902	C	ALA	A	116	21.024	25.315	25.524	1.00	39.57 C
ATOM	903	O	ALA	A	116	20.591	26.311	26.093	1.00	41.84 O
ATOM	904	CB	ALA	A	116	19.406	23.428	25.761	1.00	37.59 C
ATOM	905	N	VAL	A	117	21.711	25.374	24.396	1.00	35.34 N
ATOM	906	CA	VAL	A	117	21.907	26.651	23.736	1.00	34.85 C
ATOM	907	C	VAL	A	117	21.305	26.459	22.356	1.00	34.14 C
ATOM	908	O	VAL	A	117	21.751	25.608	21.603	1.00	35.50 O
ATOM	909	CB	VAL	A	117	23.391	26.997	23.612	1.00	40.36 C
ATOM	910	CG1	VAL	A	117	23.573	28.240	22.764	1.00	35.45 C
ATOM	911	CG2	VAL	A	117	23.957	27.265	24.994	1.00	46.40 C
ATOM	912	N	ILE	A	118	20.276	27.244	22.046	1.00	35.04 N
ATOM	913	CA	ILE	A	118	19.593	27.169	20.757	1.00	34.21 C
ATOM	914	C	ILE	A	118	20.257	28.172	19.836	1.00	25.24 C
ATOM	915	O	ILE	A	118	20.252	29.371	20.095	1.00	32.78 O
ATOM	916	CB	ILE	A	118	18.106	27.535	20.901	1.00	34.79 C
ATOM	917	CG1	ILE	A	118	17.471	26.651	21.978	1.00	43.37 C
ATOM	918	CG2	ILE	A	118	17.384	27.289	19.578	1.00	35.72 C
ATOM	919	CD1	ILE	A	118	16.071	27.043	22.340	1.00	58.55 C
ATOM	920	N	VAL	A	119	20.829	27.649	18.771	1.00	31.01 N
ATOM	921	CA	VAL	A	119	21.593	28.441	17.830	1.00	37.30 C
ATOM	922	C	VAL	A	119	20.771	29.119	16.753	1.00	37.56 C
ATOM	923	O	VAL	A	119	19.983	28.491	16.065	1.00	40.50 O
ATOM	924	CB	VAL	A	119	22.670	27.549	17.175	1.00	35.82 C
ATOM	925	CG1	VAL	A	119	23.467	28.340	16.136	1.00	34.06 C
ATOM	926	CG2	VAL	A	119	23.582	27.004	18.258	1.00	34.59 C
ATOM	927	N	CYS	A	120	20.980	30.414	16.620	1.00	36.81 N
ATOM	928	CA	CYS	A	120	20.286	31.194	15.610	1.00	32.12 C
ATOM	929	C	CYS	A	120	21.262	32.279	15.148	1.00	33.42 C
ATOM	930	O	CYS	A	120	21.534	33.244	15.873	1.00	34.81 O
ATOM	931	CB	CYS	A	120	19.027	31.819	16.211	1.00	41.13 C
ATOM	932	SG	CYS	A	120	17.972	32.754	15.028	1.00	50.41 S
ATOM	933	N	ASP	A	121	21.821	32.082	13.959	1.00	36.26 N
ATOM	934	CA	ASP	A	121	22.778	33.020	13.370	1.00	38.88 C
ATOM	935	C	ASP	A	121	22.109	33.906	12.333	1.00	36.35 C
ATOM	936	O	ASP	A	121	21.607	33.429	11.326	1.00	41.43 O
ATOM	937	CB	ASP	A	121	23.934	32.251	12.720	1.00	41.76 C
ATOM	938	CG	ASP	A	121	24.766	31.509	13.744	1.00	40.59 C
ATOM	939	OD1	ASP	A	121	25.129	32.153	14.749	1.00	47.54 O
ATOM	940	OD2	ASP	A	121	25.047	30.306	13.560	1.00	45.40 O
ATOM	941	N	VAL	A	122	22.099	35.202	12.584	1.00	41.75 N
ATOM	942	CA	VAL	A	122	21.495	36.119	11.636	1.00	52.79 C
ATOM	943	C	VAL	A	122	22.563	36.999	11.025	1.00	52.22 C
ATOM	944	O	VAL	A	122	23.670	37.115	11.550	1.00	45.91 O
ATOM	945	CB	VAL	A	122	20.458	37.052	12.302	1.00	53.37 C
ATOM	946	CG1	VAL	A	122	19.391	36.242	12.998	1.00	50.48 C
ATOM	947	CG2	VAL	A	122	21.153	37.986	13.275	1.00	58.84 C
ATOM	948	N	VAL	A	123	22.215	37.609	9.901	1.00	47.92 N
ATOM	949	CA	VAL	A	123	23.104	38.525	9.211	1.00	44.45 C
ATOM	950	C	VAL	A	123	22.279	39.739	8.809	1.00	53.24 C
ATOM	951	O	VAL	A	123	21.097	39.610	8.449	1.00	44.25 O
ATOM	952	CB	VAL	A	123	23.713	37.910	7.941	1.00	53.12 C
ATOM	953	CG1	VAL	A	123	24.633	36.758	8.307	1.00	58.99 C

Table 2

ATOM	954	CG2	VAL	A	123	22.610	37.442	7.012	1.00	54.51	C
ATOM	955	N	SER	A	124	22.911	40.906	8.893	1.00	38.99	N
ATOM	956	CA	SER	A	124	22.304	42.181	8.537	1.00	42.72	C
ATOM	957	C	SER	A	124	23.383	43.252	8.618	1.00	46.36	C
ATOM	958	O	SER	A	124	24.311	43.139	9.420	1.00	48.23	O
ATOM	959	CB	SER	A	124	21.169	42.533	9.496	1.00	45.26	C
ATOM	960	OG	SER	A	124	21.642	42.618	10.828	1.00	50.88	O
ATOM	961	N	SER	A	125	23.257	44.283	7.787	1.00	48.24	N
ATOM	962	CA	SER	A	125	24.221	45.387	7.755	1.00	54.08	C
ATOM	963	C	SER	A	125	24.173	46.098	9.081	1.00	53.53	C
ATOM	964	O	SER	A	125	25.201	46.357	9.694	1.00	54.81	O
ATOM	965	CB	SER	A	125	23.874	46.373	6.641	1.00	45.61	C
ATOM	966	OG	SER	A	125	23.901	45.724	5.391	1.00	46.33	O
ATOM	967	N	LEU	A	126	22.961	46.408	9.519	1.00	51.93	N
ATOM	968	CA	LEU	A	126	22.756	47.077	10.795	1.00	60.20	C
ATOM	969	C	LEU	A	126	22.575	46.030	11.889	1.00	63.51	C
ATOM	970	O	LEU	A	126	22.012	44.961	11.657	1.00	63.28	O
ATOM	971	CB	LEU	A	126	21.521	47.987	10.726	1.00	67.31	C
ATOM	972	CG	LEU	A	126	21.606	49.171	9.746	1.00	75.52	C
ATOM	973	CD1	LEU	A	126	20.323	49.998	9.750	1.00	66.85	C
ATOM	974	CD2	LEU	A	126	22.791	50.045	10.141	1.00	72.14	C
ATOM	975	N	PRO	A	127	23.071	46.308	13.096	1.00	69.25	N
ATOM	976	CA	PRO	A	127	22.925	45.331	14.185	1.00	64.19	C
ATOM	977	C	PRO	A	127	21.463	45.007	14.524	1.00	57.99	C
ATOM	978	O	PRO	A	127	20.655	45.913	14.728	1.00	62.20	O
ATOM	979	CB	PRO	A	127	23.701	45.950	15.354	1.00	64.92	C
ATOM	980	CG	PRO	A	127	23.957	47.367	14.952	1.00	66.17	C
ATOM	981	CD	PRO	A	127	23.849	47.492	13.478	1.00	65.55	C
ATOM	982	N	PRO	A	128	21.126	43.698	14.610	1.00	61.71	N
ATOM	983	CA	PRO	A	128	19.782	43.195	14.906	1.00	61.85	C
ATOM	984	C	PRO	A	128	19.470	43.143	16.362	1.00	62.11	C
ATOM	985	O	PRO	A	128	20.351	42.980	17.192	1.00	64.26	O
ATOM	986	CB	PRO	A	128	19.805	41.776	14.340	1.00	58.63	C
ATOM	987	CG	PRO	A	128	21.070	41.714	13.493	1.00	66.61	C
ATOM	988	CD	PRO	A	128	22.009	42.561	14.287	1.00	51.57	C
ATOM	989	N	THR	A	129	18.196	43.270	16.669	1.00	56.05	N
ATOM	990	CA	THR	A	129	17.759	43.128	18.039	1.00	50.88	C
ATOM	991	C	THR	A	129	17.038	41.791	17.944	1.00	47.70	C
ATOM	992	O	THR	A	129	16.192	41.597	17.072	1.00	52.86	O
ATOM	993	CB	THR	A	129	16.801	44.243	18.457	1.00	59.29	C
ATOM	994	OG1	THR	A	129	17.564	45.360	18.933	1.00	64.98	O
ATOM	995	CG2	THR	A	129	15.885	43.769	19.562	1.00	68.98	C
ATOM	996	N	ILE	A	130	17.377	40.868	18.827	1.00	47.42	N
ATOM	997	CA	ILE	A	130	16.793	39.543	18.779	1.00	49.45	C
ATOM	998	C	ILE	A	130	15.829	39.251	19.914	1.00	48.06	C
ATOM	999	O	ILE	A	130	16.119	39.539	21.074	1.00	49.48	O
ATOM	1000	CB	ILE	A	130	17.907	38.480	18.805	1.00	52.16	C
ATOM	1001	CG1	ILE	A	130	18.711	38.558	17.510	1.00	55.93	C
ATOM	1002	CG2	ILE	A	130	17.317	37.091	19.030	1.00	46.63	C
ATOM	1003	CD1	ILE	A	130	17.934	38.126	16.313	1.00	58.84	C
ATOM	1004	N	ILE	A	131	14.681	38.675	19.568	1.00	45.61	N
ATOM	1005	CA	ILE	A	131	13.707	38.318	20.588	1.00	50.29	C
ATOM	1006	C	ILE	A	131	13.352	36.859	20.427	1.00	33.83	C
ATOM	1007	O	ILE	A	131	12.993	36.426	19.330	1.00	50.28	O
ATOM	1008	CB	ILE	A	131	12.374	39.104	20.474	1.00	55.23	C
ATOM	1009	CG1	ILE	A	131	12.620	40.610	20.479	1.00	61.34	C
ATOM	1010	CG2	ILE	A	131	11.470	38.737	21.647	1.00	58.84	C
ATOM	1011	CD1	ILE	A	131	12.630	41.236	19.085	1.00	60.34	C
ATOM	1012	N	TRP	A	132	13.437	36.108	21.520	1.00	38.49	N

ATOM	1013	CA	TRP	A	132	13.095	34.692	21.510	1.00	46.49 C
ATOM	1014	C	TRP	A	132	11.668	34.498	22.042	1.00	48.20 C
ATOM	1015	O	TRP	A	132	11.343	34.949	23.133	1.00	45.37 O
ATOM	1016	CB	TRP	A	132	14.085	33.898	22.372	1.00	39.62 C
ATOM	1017	CG	TRP	A	132	15.384	33.632	21.653	1.00	39.42 C
ATOM	1018	CD1	TRP	A	132	16.536	34.369	21.728	1.00	36.55 C
ATOM	1019	CD2	TRP	A	132	15.645	32.570	20.726	1.00	29.03 C
ATOM	1020	NE1	TRP	A	132	17.502	33.826	20.901	1.00	34.64 N
ATOM	1021	CE2	TRP	A	132	16.985	32.725	20.278	1.00	35.20 C
ATOM	1022	CE3	TRP	A	132	14.883	31.502	20.229	1.00	33.72 C
ATOM	1023	CZ2	TRP	A	132	17.572	31.848	19.364	1.00	32.11 C
ATOM	1024	CZ3	TRP	A	132	15.470	30.632	19.318	1.00	35.81 C
ATOM	1025	CH2	TRP	A	132	16.809	30.814	18.893	1.00	33.40 C
ATOM	1026	N	LYS	A	133	10.838	33.809	21.266	1.00	51.27 N
ATOM	1027	CA	LYS	A	133	9.451	33.579	21.645	1.00	57.47 C
ATOM	1028	C	LYS	A	133	9.043	32.124	21.741	1.00	59.45 C
ATOM	1029	O	LYS	A	133	9.408	31.298	20.903	1.00	53.79 O
ATOM	1030	CB	LYS	A	133	8.518	34.267	20.650	1.00	55.78 C
ATOM	1031	CG	LYS	A	133	8.672	35.771	20.593	1.00	66.61 C
ATOM	1032	CD	LYS	A	133	7.816	36.347	19.483	1.00	76.13 C
ATOM	1033	CE	LYS	A	133	7.989	37.857	19.385	1.00	82.76 C
ATOM	1034	NZ	LYS	A	133	7.076	38.469	18.372	1.00	81.20 N
ATOM	1035	N	HIS	A	134	8.274	31.824	22.781	1.00	63.05 N
ATOM	1036	CA	HIS	A	134	7.757	30.481	22.990	1.00	66.48 C
ATOM	1037	C	HIS	A	134	6.265	30.612	23.220	1.00	77.89 C
ATOM	1038	O	HIS	A	134	5.832	31.403	24.067	1.00	63.07 O
ATOM	1039	CB	HIS	A	134	8.370	29.816	24.221	1.00	70.22 C
ATOM	1040	CG	HIS	A	134	8.006	28.368	24.367	1.00	72.09 C
ATOM	1041	ND1	HIS	A	134	8.057	27.704	25.574	1.00	72.16 N
ATOM	1042	CD2	HIS	A	134	7.622	27.448	23.447	1.00	73.41 C
ATOM	1043	CE1	HIS	A	134	7.723	26.440	25.392	1.00	77.82 C
ATOM	1044	NE2	HIS	A	134	7.454	26.357	24.112	1.00	78.13 N
ATOM	1045	N	LYS	A	135	5.488	29.843	22.461	1.00	81.08 N
ATOM	1046	CA	LYS	A	135	4.034	29.850	22.574	1.00	91.79 C
ATOM	1047	C	LYS	A	135	3.435	31.264	22.532	1.00	92.61 C
ATOM	1048	O	LYS	A	135	2.397	31.511	23.139	1.00	95.56 O
ATOM	1049	CB	LYS	A	135	3.608	29.135	23.870	1.00	90.50 C
ATOM	1050	CG	LYS	A	135	3.832	29.955	25.143	1.00	96.62 C
ATOM	1051	CD	LYS	A	135	3.541	29.173	26.414	1.00	94.31 C
ATOM	1052	CE	LYS	A	135	3.714	30.058	27.643	1.00	94.84 C
ATOM	1053	NZ	LYS	A	135	3.553	29.294	28.915	1.00	95.67 N
ATOM	1054	N	GLY	A	136	4.082	32.194	21.828	1.00	91.50 N
ATOM	1055	CA	GLY	A	136	3.553	33.551	21.741	1.00	88.54 C
ATOM	1056	C	GLY	A	136	4.256	34.597	22.589	1.00	85.72 C
ATOM	1057	O	GLY	A	136	4.366	35.754	22.187	1.00	89.77 O
ATOM	1058	N	ARG	A	137	4.734	34.184	23.757	1.00	82.42 N
ATOM	1059	CA	ARG	A	137	5.426	35.064	24.698	1.00	83.81 C
ATOM	1060	C	ARG	A	137	6.867	35.398	24.329	1.00	80.74 C
ATOM	1061	O	ARG	A	137	7.372	35.029	23.272	1.00	83.63 O
ATOM	1062	CB	ARG	A	137	5.448	34.419	26.090	1.00	90.23 C
ATOM	1063	CG	ARG	A	137	4.111	34.360	26.790	1.00	99.62 C
ATOM	1064	CD	ARG	A	137	3.856	35.652	27.530	1.00	105.25 C
ATOM	1065	NE	ARG	A	137	2.445	36.009	27.526	1.00	113.79 N
ATOM	1066	CZ	ARG	A	137	1.973	37.181	27.937	1.00	114.75 C
ATOM	1067	NH1	ARG	A	137	2.805	38.109	28.390	1.00	116.01 N
ATOM	1068	NH2	ARG	A	137	0.672	37.432	27.883	1.00	117.60 N
ATOM	1069	N	ASP	A	138	7.510	36.116	25.241	1.00	76.46 N
ATOM	1070	CA	ASP	A	138	8.907	36.497	25.132	1.00	75.03 C
ATOM	1071	C	ASP	A	138	9.464	35.773	26.328	1.00	76.03 C

Table 2

ATOM	1072	O	ASP	A	138	9.139	36.102	27.476	1.00	73.85 O
ATOM	1073	CB	ASP	A	138	9.107	38.000	25.318	1.00	77.22 C
ATOM	1074	CG	ASP	A	138	10.578	38.403	25.275	1.00	77.41 C
ATOM	1075	OD1	ASP	A	138	11.410	37.736	25.931	1.00	76.27 O
ATOM	1076	OD2	ASP	A	138	10.906	39.394	24.590	1.00	67.17 O
ATOM	1077	N	VAL	A	139	10.292	34.776	26.069	1.00	63.30 N
ATOM	1078	CA	VAL	A	139	10.838	33.992	27.152	1.00	58.22 C
ATOM	1079	C	VAL	A	139	11.541	34.814	28.224	1.00	60.55 C
ATOM	1080	O	VAL	A	139	11.799	34.320	29.321	1.00	71.06 O
ATOM	1081	CB	VAL	A	139	11.785	32.935	26.595	1.00	62.13 C
ATOM	1082	CG1	VAL	A	139	11.091	32.195	25.469	1.00	55.43 C
ATOM	1083	CG2	VAL	A	139	13.068	33.588	26.091	1.00	47.09 C
ATOM	1084	N	ILE	A	140	11.841	36.070	27.918	1.00	66.18 N
ATOM	1085	CA	ILE	A	140	12.519	36.924	28.878	1.00	73.19 C
ATOM	1086	C	ILE	A	140	11.594	37.514	29.925	1.00	77.32 C
ATOM	1087	O	ILE	A	140	11.822	37.370	31.123	1.00	79.51 O
ATOM	1088	CB	ILE	A	140	13.229	38.098	28.183	1.00	75.30 C
ATOM	1089	CG1	ILE	A	140	14.357	37.569	27.300	1.00	79.57 C
ATOM	1090	CG2	ILE	A	140	13.789	39.062	29.227	1.00	84.41 C
ATOM	1091	CD1	ILE	A	140	15.381	36.752	28.065	1.00	75.80 C
ATOM	1092	N	LEU	A	141	10.553	38.194	29.468	1.00	85.78 N
ATOM	1093	CA	LEU	A	141	9.632	38.838	30.384	1.00	97.07 C
ATOM	1094	C	LEU	A	141	8.966	37.937	31.409	1.00	101.56 C
ATOM	1095	O	LEU	A	141	8.177	38.408	32.225	1.00	107.39 O
ATOM	1096	CB	LEU	A	141	8.571	39.615	29.608	1.00	101.80 C
ATOM	1097	CG	LEU	A	141	9.106	40.905	28.991	1.00	106.45 C
ATOM	1098	CD1	LEU	A	141	7.949	41.736	28.461	1.00	108.62 C
ATOM	1099	CD2	LEU	A	141	9.882	41.699	30.046	1.00	104.45 C
ATOM	1100	N	LYS	A	142	9.276	36.650	31.384	1.00	101.47 N
ATOM	1101	CA	LYS	A	142	8.689	35.751	32.362	1.00	101.64 C
ATOM	1102	C	LYS	A	142	9.660	35.560	33.527	1.00	101.85 C
ATOM	1103	O	LYS	A	142	9.262	35.339	34.675	1.00	105.32 O
ATOM	1104	CB	LYS	A	142	8.346	34.404	31.702	1.00	100.75 C
ATOM	1105	CG	LYS	A	142	9.525	33.643	31.098	1.00	98.61 C
ATOM	1106	CD	LYS	A	142	8.997	32.520	30.208	1.00	93.54 C
ATOM	1107	CE	LYS	A	142	10.082	31.550	29.747	1.00	96.37 C
ATOM	1108	NZ	LYS	A	142	9.503	30.522	28.822	1.00	91.06 N
ATOM	1109	N	LYS	A	143	10.940	35.703	33.223	1.00	102.59 N
ATOM	1110	CA	LYS	A	143	11.992	35.519	34.206	1.00	104.90 C
ATOM	1111	C	LYS	A	143	11.852	34.206	34.942	1.00	100.79 C
ATOM	1112	O	LYS	A	143	11.372	34.122	36.080	1.00	100.29 O
ATOM	1113	CB	LYS	A	143	12.059	36.672	35.207	1.00	107.17 C
ATOM	1114	CG	LYS	A	143	13.224	36.510	36.183	1.00	113.10 C
ATOM	1115	CD	LYS	A	143	14.559	36.248	35.522	1.00	116.78 C
ATOM	1116	CE	LYS	A	143	15.786	36.228	36.466	1.00	123.03 C
ATOM	1117	NZ	LYS	A	143	17.123	36.187	35.780	1.00	119.60 N
ATOM	1118	N	ASP	A	144	12.237	33.182	34.199	1.00	94.81 N
ATOM	1119	CA	ASP	A	144	12.319	31.828	34.669	1.00	85.45 C
ATOM	1120	C	ASP	A	144	13.827	31.840	34.531	1.00	79.96 C
ATOM	1121	O	ASP	A	144	14.365	31.687	33.436	1.00	88.63 O
ATOM	1122	CB	ASP	A	144	11.718	30.833	33.677	1.00	85.69 C
ATOM	1123	CG	ASP	A	144	11.884	29.398	34.137	1.00	89.87 C
ATOM	1124	OD1	ASP	A	144	12.989	29.060	34.609	1.00	90.66 O
ATOM	1125	OD2	ASP	A	144	10.913	28.608	34.041	1.00	101.36 O
ATOM	1126	N	VAL	A	145	14.490	32.118	35.642	1.00	68.69 N
ATOM	1127	CA	VAL	A	145	15.946	32.226	35.721	1.00	67.87 C
ATOM	1128	C	VAL	A	145	16.758	31.316	34.795	1.00	55.99 C
ATOM	1129	O	VAL	A	145	17.915	31.598	34.490	1.00	61.04 O
ATOM	1130	CB	VAL	A	145	16.415	31.974	37.167	1.00	76.83 C

Table 2

ATOM	1131	CG1	VAL	A	145	15.901	33.082	38.076	1.00	76.29 C
ATOM	1132	CG2	VAL	A	145	15.902	30.617	37.655	1.00	77.74 C
ATOM	1133	N	ARG	A	146	16.148	30.227	34.349	1.00	52.68 N
ATOM	1134	CA	ARG	A	146	16.839	29.283	33.493	1.00	56.85 C
ATOM	1135	C	ARG	A	146	16.984	29.771	32.055	1.00	48.40 C
ATOM	1136	O	ARG	A	146	17.808	29.258	31.311	1.00	46.31 O
ATOM	1137	CB	ARG	A	146	16.121	27.925	33.538	1.00	44.42 C
ATOM	1138	CG	ARG	A	146	16.235	27.242	34.901	1.00	53.27 C
ATOM	1139	CD	ARG	A	146	15.613	25.846	34.911	1.00	47.00 C
ATOM	1140	NE	ARG	A	146	14.253	25.864	34.388	1.00	43.57 N
ATOM	1141	CZ	ARG	A	146	13.898	25.279	33.253	1.00	53.19 C
ATOM	1142	NH1	ARG	A	146	14.810	24.627	32.533	1.00	46.06 N
ATOM	1143	NH2	ARG	A	146	12.646	25.359	32.825	1.00	49.59 N
ATOM	1144	N	PHE	A	147	16.190	30.766	31.680	1.00	49.96 N
ATOM	1145	CA	PHE	A	147	16.233	31.297	30.330	1.00	55.08 C
ATOM	1146	C	PHE	A	147	17.068	32.568	30.213	1.00	55.40 C
ATOM	1147	O	PHE	A	147	16.837	33.551	30.916	1.00	58.84 O
ATOM	1148	CB	PHE	A	147	14.815	31.536	29.828	1.00	47.49 C
ATOM	1149	CG	PHE	A	147	14.003	30.271	29.679	1.00	55.00 C
ATOM	1150	CD1	PHE	A	147	13.520	29.598	30.796	1.00	50.35 C
ATOM	1151	CD2	PHE	A	147	13.730	29.747	28.416	1.00	49.95 C
ATOM	1152	CE1	PHE	A	147	12.773	28.416	30.654	1.00	61.13 C
ATOM	1153	CE2	PHE	A	147	12.986	28.571	28.265	1.00	53.83 C
ATOM	1154	CZ	PHE	A	147	12.508	27.905	29.386	1.00	56.75 C
ATOM	1155	N	ILE	A	148	18.038	32.536	29.307	1.00	50.18 N
ATOM	1156	CA	ILE	A	148	18.940	33.661	29.097	1.00	53.42 C
ATOM	1157	C	ILE	A	148	19.348	33.856	27.636	1.00	45.25 C
ATOM	1158	O	ILE	A	148	19.659	32.899	26.944	1.00	44.46 O
ATOM	1159	CB	ILE	A	148	20.233	33.463	29.908	1.00	55.68 C
ATOM	1160	CG1	ILE	A	148	19.907	33.427	31.399	1.00	65.94 C
ATOM	1161	CG2	ILE	A	148	21.231	34.573	29.597	1.00	61.53 C
ATOM	1162	CD1	ILE	A	148	21.093	33.081	32.279	1.00	69.07 C
ATOM	1163	N	VAL	A	149	19.337	35.099	27.172	1.00	37.73 N
ATOM	1164	CA	VAL	A	149	19.764	35.381	25.817	1.00	42.64 C
ATOM	1165	C	VAL	A	149	21.236	35.794	25.962	1.00	46.84 C
ATOM	1166	O	VAL	A	149	21.552	36.756	26.655	1.00	47.29 O
ATOM	1167	CB	VAL	A	149	18.929	36.512	25.185	1.00	42.61 C
ATOM	1168	CG1	VAL	A	149	19.472	36.844	23.791	1.00	44.21 C
ATOM	1169	CG2	VAL	A	149	17.444	36.067	25.064	1.00	43.57 C
ATOM	1170	N	LEU	A	150	22.127	35.036	25.328	1.00	40.34 N
ATOM	1171	CA	LEU	A	150	23.568	35.289	25.400	1.00	42.16 C
ATOM	1172	C	LEU	A	150	24.030	36.450	24.524	1.00	47.24 C
ATOM	1173	O	LEU	A	150	23.262	36.965	23.723	1.00	39.70 O
ATOM	1174	CB	LEU	A	150	24.305	34.019	25.001	1.00	36.82 C
ATOM	1175	CG	LEU	A	150	23.885	32.825	25.860	1.00	50.79 C
ATOM	1176	CD1	LEU	A	150	24.330	31.505	25.225	1.00	45.07 C
ATOM	1177	CD2	LEU	A	150	24.473	32.999	27.252	1.00	55.15 C
ATOM	1178	N	SER	A	151	25.295	36.849	24.666	1.00	50.63 N
ATOM	1179	CA	SER	A	151	25.849	37.953	23.880	1.00	44.74 C
ATOM	1180	C	SER	A	151	25.770	37.710	22.365	1.00	37.06 C
ATOM	1181	O	SER	A	151	25.651	38.663	21.587	1.00	49.84 O
ATOM	1182	CB	SER	A	151	27.320	38.200	24.273	1.00	45.09 C
ATOM	1183	OG	SER	A	151	28.150	37.144	23.792	1.00	45.86 O
ATOM	1184	N	ASN	A	152	25.866	36.455	21.937	1.00	38.65 N
ATOM	1185	CA	ASN	A	152	25.784	36.140	20.506	1.00	40.49 C
ATOM	1186	C	ASN	A	152	24.321	35.998	20.073	1.00	40.22 C
ATOM	1187	O	ASN	A	152	24.036	35.583	18.936	1.00	34.75 O
ATOM	1188	CB	ASN	A	152	26.476	34.821	20.207	1.00	39.82 C
ATOM	1189	CG	ASN	A	152	26.097	33.752	21.199	1.00	54.90 C

Table 2

ATOM	1190	OD1	ASN	A	152	24.972	33.739	21.694	1.00	45.34 O
ATOM	1191	ND2	ASN	A	152	27.029	32.850	21.504	1.00	46.13 N
ATOM	1192	N	ASN	A	153	23.410	36.309	20.990	1.00	38.94 N
ATOM	1193	CA	ASN	A	153	21.969	36.213	20.740	1.00	45.44 C
ATOM	1194	C	ASN	A	153	21.352	34.827	20.723	1.00	42.99 C
ATOM	1195	O	ASN	A	153	20.171	34.674	20.414	1.00	38.19 O
ATOM	1196	CB	ASN	A	153	21.589	36.964	19.469	1.00	42.88 C
ATOM	1197	CG	ASN	A	153	21.665	38.468	19.660	1.00	49.74 C
ATOM	1198	OD1	ASN	A	153	21.300	38.990	20.720	1.00	57.35 O
ATOM	1199	ND2	ASN	A	153	22.130	39.171	18.645	1.00	53.13 N
ATOM	1200	N	TYR	A	154	22.121	33.810	21.080	1.00	31.78 N
ATOM	1201	CA	TYR	A	154	21.563	32.463	21.151	1.00	37.05 C
ATOM	1202	C	TYR	A	154	20.707	32.352	22.418	1.00	36.11 C
ATOM	1203	O	TYR	A	154	20.918	33.107	23.357	1.00	35.56 O
ATOM	1204	CB	TYR	A	154	22.675	31.425	21.247	1.00	35.50 C
ATOM	1205	CG	TYR	A	154	23.535	31.329	20.021	1.00	40.10 C
ATOM	1206	CD1	TYR	A	154	24.703	30.565	20.037	1.00	33.69 C
ATOM	1207	CD2	TYR	A	154	23.179	31.990	18.837	1.00	35.06 C
ATOM	1208	CE1	TYR	A	154	25.505	30.457	18.899	1.00	38.35 C
ATOM	1209	CE2	TYR	A	154	23.979	31.892	17.676	1.00	34.58 C
ATOM	1210	CZ	TYR	A	154	25.143	31.119	17.726	1.00	46.30 C
ATOM	1211	OH	TYR	A	154	25.954	31.005	16.618	1.00	43.90 O
ATOM	1212	N	LEU	A	155	19.757	31.415	22.450	1.00	37.10 N
ATOM	1213	CA	LEU	A	155	18.936	31.237	23.650	1.00	33.06 C
ATOM	1214	C	LEU	A	155	19.514	30.121	24.496	1.00	25.37 C
ATOM	1215	O	LEU	A	155	19.688	28.989	24.037	1.00	33.57 O
ATOM	1216	CB	LEU	A	155	17.482	30.866	23.303	1.00	33.13 C
ATOM	1217	CG	LEU	A	155	16.635	30.561	24.545	1.00	39.86 C
ATOM	1218	CD1	LEU	A	155	16.673	31.752	25.480	1.00	39.38 C
ATOM	1219	CD2	LEU	A	155	15.185	30.269	24.142	1.00	35.14 C
ATOM	1220	N	GLN	A	156	19.802	30.437	25.746	1.00	34.79 N
ATOM	1221	CA	GLN	A	156	20.327	29.432	26.638	1.00	30.99 C
ATOM	1222	C	GLN	A	156	19.212	28.964	27.568	1.00	33.82 C
ATOM	1223	O	GLN	A	156	18.545	29.792	28.205	1.00	38.51 O
ATOM	1224	CB	GLN	A	156	21.454	30.010	27.507	1.00	36.98 C
ATOM	1225	CG	GLN	A	156	22.028	28.974	28.478	1.00	52.10 C
ATOM	1226	CD	GLN	A	156	23.034	29.556	29.461	1.00	59.17 C
ATOM	1227	OE1	GLN	A	156	22.750	30.542	30.134	1.00	58.98 O
ATOM	1228	NE2	GLN	A	156	24.207	28.934	29.558	1.00	56.95 N
ATOM	1229	N	ILE	A	157	19.012	27.651	27.655	1.00	35.15 N
ATOM	1230	CA	ILE	A	157	18.001	27.104	28.570	1.00	39.14 C
ATOM	1231	C	ILE	A	157	18.737	26.177	29.530	1.00	40.54 C
ATOM	1232	O	ILE	A	157	19.028	25.030	29.189	1.00	41.38 O
ATOM	1233	CB	ILE	A	157	16.928	26.304	27.832	1.00	36.32 C
ATOM	1234	CG1	ILE	A	157	16.195	27.208	26.843	1.00	32.60 C
ATOM	1235	CG2	ILE	A	157	15.943	25.728	28.842	1.00	42.84 C
ATOM	1236	CD1	ILE	A	157	15.181	26.458	25.983	1.00	40.70 C
ATOM	1237	N	ARG	A	158	19.068	26.674	30.718	1.00	38.99 N
ATOM	1238	CA	ARG	A	158	19.804	25.857	31.673	1.00	45.51 C
ATOM	1239	C	ARG	A	158	18.982	24.711	32.273	1.00	43.75 C
ATOM	1240	O	ARG	A	158	17.781	24.851	32.484	1.00	47.32 O
ATOM	1241	CB	ARG	A	158	20.381	26.749	32.778	1.00	53.96 C
ATOM	1242	CG	ARG	A	158	21.475	27.697	32.272	1.00	70.32 C
ATOM	1243	CD	ARG	A	158	22.155	28.453	33.405	1.00	65.23 C
ATOM	1244	NE	ARG	A	158	21.287	29.449	34.012	1.00	68.48 N
ATOM	1245	CZ	ARG	A	158	21.572	30.079	35.147	1.00	75.70 C
ATOM	1246	NH1	ARG	A	158	22.704	29.808	35.792	1.00	65.00 N
ATOM	1247	NH2	ARG	A	158	20.724	30.973	35.641	1.00	71.67 N
ATOM	1248	N	GLY	A	159	19.653	23.589	32.544	1.00	47.20 N

ATOM	1249	CA	GLY	A	159	18.998	22.415	33.096	1.00	48.68 C
ATOM	1250	C	GLY	A	159	17.731	22.133	32.317	1.00	50.27 C
ATOM	1251	O	GLY	A	159	16.658	21.983	32.897	1.00	44.17 O
ATOM	1252	N	ILE	A	160	17.847	22.050	30.997	1.00	46.11 N
ATOM	1253	CA	ILE	A	160	16.664	21.831	30.189	1.00	39.12 C
ATOM	1254	C	ILE	A	160	15.872	20.590	30.606	1.00	46.02 C
ATOM	1255	O	ILE	A	160	16.434	19.514	30.840	1.00	35.03 O
ATOM	1256	CB	ILE	A	160	17.013	21.755	28.702	1.00	34.52 C
ATOM	1257	CG1	ILE	A	160	15.727	21.917	27.874	1.00	37.12 C
ATOM	1258	CG2	ILE	A	160	17.679	20.446	28.376	1.00	34.14 C
ATOM	1259	CD1	ILE	A	160	15.993	22.199	26.392	1.00	28.22 C
ATOM	1260	N	LYS	A	161	14.557	20.767	30.692	1.00	42.18 N
ATOM	1261	CA	LYS	A	161	13.631	19.710	31.089	1.00	47.02 C
ATOM	1262	C	LYS	A	161	12.855	19.202	29.899	1.00	43.66 C
ATOM	1263	O	LYS	A	161	12.686	19.908	28.899	1.00	41.53 O
ATOM	1264	CB	LYS	A	161	12.599	20.236	32.095	1.00	49.68 C
ATOM	1265	CG	LYS	A	161	13.156	20.896	33.337	1.00	55.48 C
ATOM	1266	CD	LYS	A	161	12.002	21.450	34.178	1.00	65.12 C
ATOM	1267	CE	LYS	A	161	12.488	22.175	35.421	1.00	70.60 C
ATOM	1268	NZ	LYS	A	161	11.350	22.563	36.307	1.00	76.58 N
ATOM	1269	N	LYS	A	162	12.353	17.982	30.020	1.00	44.57 N
ATOM	1270	CA	LYS	A	162	11.560	17.383	28.956	1.00	47.82 C
ATOM	1271	C	LYS	A	162	10.372	18.311	28.670	1.00	43.43 C
ATOM	1272	O	LYS	A	162	9.914	18.427	27.535	1.00	44.67 O
ATOM	1273	CB	LYS	A	162	11.084	15.987	29.391	1.00	50.56 C
ATOM	1274	CG	LYS	A	162	10.298	15.208	28.339	1.00	50.30 C
ATOM	1275	CD	LYS	A	162	11.109	14.958	27.085	1.00	52.43 C
ATOM	1276	CE	LYS	A	162	10.279	14.227	26.051	1.00	60.58 C
ATOM	1277	NZ	LYS	A	162	10.963	14.149	24.731	1.00	59.55 N
ATOM	1278	N	THR	A	163	9.897	19.010	29.691	1.00	44.12 N
ATOM	1279	CA	THR	A	163	8.764	19.904	29.487	1.00	53.06 C
ATOM	1280	C	THR	A	163	9.140	21.234	28.833	1.00	55.60 C
ATOM	1281	O	THR	A	163	8.294	22.107	28.676	1.00	50.18 O
ATOM	1282	CB	THR	A	163	8.022	20.195	30.812	1.00	53.57 C
ATOM	1283	OG1	THR	A	163	8.942	20.712	31.780	1.00	55.40 O
ATOM	1284	CG2	THR	A	163	7.372	18.914	31.349	1.00	55.53 C
ATOM	1285	N	ASP	A	164	10.407	21.397	28.465	1.00	48.62 N
ATOM	1286	CA	ASP	A	164	10.826	22.628	27.810	1.00	42.03 C
ATOM	1287	C	ASP	A	164	10.764	22.477	26.299	1.00	44.90 C
ATOM	1288	O	ASP	A	164	10.821	23.470	25.573	1.00	48.57 O
ATOM	1289	CB	ASP	A	164	12.260	23.017	28.209	1.00	38.06 C
ATOM	1290	CG	ASP	A	164	12.358	23.525	29.631	1.00	36.69 C
ATOM	1291	OD1	ASP	A	164	11.469	24.295	30.052	1.00	49.63 O
ATOM	1292	OD2	ASP	A	164	13.337	23.168	30.327	1.00	44.71 O
ATOM	1293	N	GLU	A	165	10.639	21.251	25.798	1.00	44.64 N
ATOM	1294	CA	GLU	A	165	10.602	21.116	24.353	1.00	53.09 C
ATOM	1295	C	GLU	A	165	9.396	21.821	23.739	1.00	49.63 C
ATOM	1296	O	GLU	A	165	8.465	22.215	24.440	1.00	52.65 O
ATOM	1297	CB	GLU	A	165	10.681	19.650	23.909	1.00	50.75 C
ATOM	1298	CG	GLU	A	165	9.828	18.702	24.683	1.00	65.76 C
ATOM	1299	CD	GLU	A	165	9.940	17.283	24.155	1.00	72.74 C
ATOM	1300	OE1	GLU	A	165	11.040	16.884	23.691	1.00	69.18 O
ATOM	1301	OE2	GLU	A	165	8.922	16.565	24.220	1.00	65.52 O
ATOM	1302	N	GLY	A	166	9.451	22.002	22.424	1.00	48.94 N
ATOM	1303	CA	GLY	A	166	8.405	22.700	21.701	1.00	55.73 C
ATOM	1304	C	GLY	A	166	9.067	23.579	20.655	1.00	47.37 C
ATOM	1305	O	GLY	A	166	10.256	23.419	20.340	1.00	47.39 O
ATOM	1306	N	THR	A	167	8.317	24.517	20.112	0.50	34.99 N
ATOM	1307	CA	THR	A	167	8.865	25.386	19.099	0.50	35.61 C

Table 2

ATOM	1308	C	THR	A	167	9.253	26.706	19.720	0.50	31.90	C
ATOM	1309	O	THR	A	167	8.524	27.264	20.526	0.50	30.91	O
ATOM	1310	CB	THR	A	167	7.849	25.623	18.006	0.50	40.53	C
ATOM	1311	OG1	THR	A	167	6.633	26.081	18.602	0.50	51.84	O
ATOM	1312	CG2	THR	A	167	7.574	24.332	17.258	0.50	26.00	C
ATOM	1313	N	TYR	A	168	10.434	27.191	19.360	1.00	43.71	N
ATOM	1314	CA	TYR	A	168	10.922	28.467	19.871	1.00	42.97	C
ATOM	1315	C	TYR	A	168	11.183	29.372	18.689	1.00	38.98	C
ATOM	1316	O	TYR	A	168	11.801	28.965	17.705	1.00	43.48	O
ATOM	1317	CB	TYR	A	168	12.205	28.283	20.682	1.00	44.02	C
ATOM	1318	CG	TYR	A	168	11.968	27.702	22.047	1.00	36.86	C
ATOM	1319	CD1	TYR	A	168	11.676	26.353	22.206	1.00	38.88	C
ATOM	1320	CD2	TYR	A	168	12.000	28.512	23.179	1.00	36.72	C
ATOM	1321	CE1	TYR	A	168	11.419	25.821	23.466	1.00	41.93	C
ATOM	1322	CE2	TYR	A	168	11.739	27.997	24.440	1.00	42.88	C
ATOM	1323	CZ	TYR	A	168	11.451	26.652	24.576	1.00	43.41	C
ATOM	1324	OH	TYR	A	168	11.193	26.139	25.824	1.00	40.88	O
ATOM	1325	N	ARG	A	169	10.715	30.610	18.787	1.00	44.05	N
ATOM	1326	CA	ARG	A	169	10.871	31.533	17.681	1.00	41.18	C
ATOM	1327	C	ARG	A	169	12.013	32.526	17.868	1.00	36.73	C
ATOM	1328	O	ARG	A	169	12.102	33.216	18.877	1.00	40.52	O
ATOM	1329	CB	ARG	A	169	9.552	32.289	17.444	1.00	50.40	C
ATOM	1330	CG	ARG	A	169	9.655	33.416	16.430	1.00	60.69	C
ATOM	1331	CD	ARG	A	169	8.284	33.861	15.925	1.00	46.23	C
ATOM	1332	NE	ARG	A	169	7.716	32.865	15.022	1.00	56.58	N
ATOM	1333	CZ	ARG	A	169	6.535	32.984	14.420	1.00	71.77	C
ATOM	1334	NH1	ARG	A	169	5.785	34.064	14.621	1.00	58.65	N
ATOM	1335	NH2	ARG	A	169	6.101	32.015	13.618	1.00	59.89	N
ATOM	1336	N	CYS	A	170	12.888	32.576	16.875	1.00	42.37	N
ATOM	1337	CA	CYS	A	170	13.998	33.506	16.919	1.00	45.65	C
ATOM	1338	C	CYS	A	170	13.546	34.667	16.025	1.00	31.99	C
ATOM	1339	O	CYS	A	170	13.423	34.505	14.810	1.00	41.21	O
ATOM	1340	CB	CYS	A	170	15.253	32.840	16.357	1.00	42.01	C
ATOM	1341	SG	CYS	A	170	16.748	33.898	16.241	1.00	52.42	S
ATOM	1342	N	GLU	A	171	13.289	35.820	16.635	1.00	44.29	N
ATOM	1343	CA	GLU	A	171	12.830	36.978	15.879	1.00	49.65	C
ATOM	1344	C	GLU	A	171	13.814	38.129	15.844	1.00	40.68	C
ATOM	1345	O	GLU	A	171	14.218	38.663	16.885	1.00	45.31	O
ATOM	1346	CB	GLU	A	171	11.503	37.502	16.426	1.00	47.28	C
ATOM	1347	CG	GLU	A	171	10.905	38.616	15.560	1.00	57.47	C
ATOM	1348	CD	GLU	A	171	9.580	39.147	16.096	1.00	65.00	C
ATOM	1349	OE1	GLU	A	171	9.593	39.989	17.028	1.00	62.15	O
ATOM	1350	OE2	GLU	A	171	8.531	38.707	15.584	1.00	54.66	O
ATOM	1351	N	GLY	A	172	14.163	38.525	14.625	1.00	46.09	N
ATOM	1352	CA	GLY	A	172	15.086	39.624	14.436	1.00	49.63	C
ATOM	1353	C	GLY	A	172	14.388	40.872	13.930	1.00	46.92	C
ATOM	1354	O	GLY	A	172	13.557	40.812	13.014	1.00	50.71	O
ATOM	1355	N	ARG	A	173	14.753	41.998	14.535	1.00	40.06	N
ATOM	1356	CA	ARG	A	173	14.222	43.309	14.215	1.00	44.00	C
ATOM	1357	C	ARG	A	173	15.335	44.350	14.038	1.00	56.42	C
ATOM	1358	O	ARG	A	173	16.328	44.354	14.768	1.00	47.64	O
ATOM	1359	CB	ARG	A	173	13.310	43.800	15.345	1.00	42.90	C
ATOM	1360	CG	ARG	A	173	12.048	42.970	15.527	1.00	41.21	C
ATOM	1361	CD	ARG	A	173	11.096	43.649	16.488	1.00	49.33	C
ATOM	1362	NE	ARG	A	173	9.880	42.862	16.656	1.00	55.21	N
ATOM	1363	CZ	ARG	A	173	8.669	43.387	16.790	1.00	54.70	C
ATOM	1364	NH1	ARG	A	173	8.518	44.704	16.773	1.00	54.11	N
ATOM	1365	NH2	ARG	A	173	7.610	42.596	16.935	1.00	54.36	N
ATOM	1366	N	ILE	A	174	15.135	45.245	13.080	1.00	51.94	N

Table 2

ATOM	1367	CA	ILE	A	174	16.068	46.331	12.821	1.00	48.52 C
ATOM	1368	C	ILE	A	174	15.228	47.591	12.902	1.00	42.65 C
ATOM	1369	O	ILE	A	174	14.485	47.901	11.973	1.00	40.81 O
ATOM	1370	CB	ILE	A	174	16.687	46.193	11.436	1.00	51.33 C
ATOM	1371	CG1	ILE	A	174	17.536	44.921	11.395	1.00	62.03 C
ATOM	1372	CG2	ILE	A	174	17.536	47.417	11.128	1.00	57.79 C
ATOM	1373	CD1	ILE	A	174	18.075	44.586	10.042	1.00	60.04 C
ATOM	1374	N	LEU	A	175	15.348	48.327	14.004	1.00	43.83 N
ATOM	1375	CA	LEU	A	175	14.514	49.513	14.203	1.00	50.67 C
ATOM	1376	C	LEU	A	175	14.502	50.558	13.102	1.00	53.85 C
ATOM	1377	O	LEU	A	175	13.435	51.017	12.694	1.00	54.58 O
ATOM	1378	CB	LEU	A	175	14.853	50.223	15.520	1.00	52.93 C
ATOM	1379	CG	LEU	A	175	14.067	51.544	15.693	1.00	69.90 C
ATOM	1380	CD1	LEU	A	175	12.539	51.287	15.592	1.00	58.23 C
ATOM	1381	CD2	LEU	A	175	14.423	52.195	17.026	1.00	61.03 C
ATOM	1382	N	ALA	A	176	15.681	50.962	12.641	1.00	49.99 N
ATOM	1383	CA	ALA	A	176	15.753	51.981	11.605	1.00	51.23 C
ATOM	1384	C	ALA	A	176	14.902	51.629	10.385	1.00	45.44 C
ATOM	1385	O	ALA	A	176	14.347	52.518	9.739	1.00	57.30 O
ATOM	1386	CB	ALA	A	176	17.211	52.214	11.193	1.00	54.86 C
ATOM	1387	N	ARG	A	177	14.776	50.341	10.074	1.00	50.42 N
ATOM	1388	CA	ARG	A	177	13.987	49.924	8.917	1.00	45.08 C
ATOM	1389	C	ARG	A	177	12.641	49.302	9.269	1.00	48.67 C
ATOM	1390	O	ARG	A	177	11.862	48.974	8.377	1.00	45.39 O
ATOM	1391	CB	ARG	A	177	14.778	48.918	8.081	1.00	57.24 C
ATOM	1392	CG	ARG	A	177	16.084	49.467	7.544	1.00	64.35 C
ATOM	1393	CD	ARG	A	177	16.813	48.460	6.666	1.00	64.31 C
ATOM	1394	NE	ARG	A	177	17.880	49.138	5.939	1.00	77.29 N
ATOM	1395	CZ	ARG	A	177	17.889	49.331	4.625	1.00	58.44 C
ATOM	1396	NH1	ARG	A	177	16.892	48.883	3.873	1.00	54.23 N
ATOM	1397	NH2	ARG	A	177	18.884	50.009	4.074	1.00	72.33 N
ATOM	1398	N	GLY	A	178	12.373	49.130	10.562	1.00	44.96 N
ATOM	1399	CA	GLY	A	178	11.122	48.508	10.972	1.00	44.41 C
ATOM	1400	C	GLY	A	178	11.050	47.122	10.354	1.00	44.68 C
ATOM	1401	O	GLY	A	178	9.976	46.574	10.092	1.00	40.98 O
ATOM	1402	N	GLU	A	179	12.227	46.544	10.146	1.00	41.13 N
ATOM	1403	CA	GLU	A	179	12.363	45.240	9.513	1.00	46.62 C
ATOM	1404	C	GLU	A	179	12.204	44.076	10.496	1.00	46.51 C
ATOM	1405	O	GLU	A	179	12.710	44.116	11.619	1.00	46.07 O
ATOM	1406	CB	GLU	A	179	13.736	45.192	8.817	1.00	47.47 C
ATOM	1407	CG	GLU	A	179	14.011	44.049	7.852	1.00	52.61 C
ATOM	1408	CD	GLU	A	179	15.396	44.199	7.186	1.00	67.97 C
ATOM	1409	OE1	GLU	A	179	16.232	44.974	7.709	1.00	52.50 O
ATOM	1410	OE2	GLU	A	179	15.657	43.540	6.156	1.00	61.67 O
ATOM	1411	N	ILE	A	180	11.504	43.037	10.044	1.00	46.98 N
ATOM	1412	CA	ILE	A	180	11.260	41.843	10.844	1.00	44.57 C
ATOM	1413	C	ILE	A	180	11.442	40.596	10.028	1.00	49.88 C
ATOM	1414	O	ILE	A	180	11.018	40.531	8.878	1.00	50.41 O
ATOM	1415	CB	ILE	A	180	9.820	41.784	11.371	1.00	60.91 C
ATOM	1416	CG1	ILE	A	180	9.586	42.889	12.387	1.00	56.28 C
ATOM	1417	CG2	ILE	A	180	9.544	40.416	11.996	1.00	58.36 C
ATOM	1418	CD1	ILE	A	180	8.206	42.834	12.973	1.00	63.77 C
ATOM	1419	N	ASN	A	181	12.088	39.607	10.632	1.00	49.49 N
ATOM	1420	CA	ASN	A	181	12.269	38.308	10.010	1.00	44.31 C
ATOM	1421	C	ASN	A	181	12.329	37.382	11.223	1.00	53.84 C
ATOM	1422	O	ASN	A	181	12.789	37.776	12.297	1.00	49.42 O
ATOM	1423	CB	ASN	A	181	13.555	38.240	9.189	1.00	50.86 C
ATOM	1424	CG	ASN	A	181	13.527	37.117	8.165	1.00	58.63 C
ATOM	1425	OD1	ASN	A	181	12.581	36.332	8.126	1.00	68.55 O

ATOM	1426	ND2	ASN	A	181	14.567	37.031	7.331	1.00	62.99	N
ATOM	1427	N	PHE	A	182	11.818	36.172	11.082	1.00	51.66	N
ATOM	1428	CA	PHE	A	182	11.839	35.261	12.210	1.00	54.82	C
ATOM	1429	C	PHE	A	182	12.052	33.843	11.711	1.00	62.75	C
ATOM	1430	O	PHE	A	182	11.914	33.563	10.512	1.00	55.35	O
ATOM	1431	CB	PHE	A	182	10.521	35.354	12.989	1.00	62.28	C
ATOM	1432	CG	PHE	A	182	9.352	34.717	12.283	1.00	74.94	C
ATOM	1433	CD1	PHE	A	182	9.292	33.333	12.120	1.00	82.11	C
ATOM	1434	CD2	PHE	A	182	8.333	35.496	11.745	1.00	81.28	C
ATOM	1435	CE1	PHE	A	182	8.244	32.733	11.429	1.00	84.02	C
ATOM	1436	CE2	PHE	A	182	7.276	34.901	11.049	1.00	84.09	C
ATOM	1437	CZ	PHE	A	182	7.236	33.516	10.892	1.00	83.03	C
ATOM	1438	N	LYS	A	183	12.388	32.946	12.633	1.00	58.39	N
ATOM	1439	CA	LYS	A	183	12.591	31.541	12.295	1.00	50.63	C
ATOM	1440	C	LYS	A	183	12.106	30.678	13.459	1.00	53.23	C
ATOM	1441	O	LYS	A	183	12.431	30.947	14.622	1.00	45.57	O
ATOM	1442	CB	LYS	A	183	14.073	31.263	12.022	1.00	65.15	C
ATOM	1443	CG	LYS	A	183	14.446	29.780	11.957	1.00	64.65	C
ATOM	1444	CD	LYS	A	183	14.295	29.166	10.566	1.00	63.11	C
ATOM	1445	CE	LYS	A	183	14.627	27.670	10.590	1.00	53.42	C
ATOM	1446	NZ	LYS	A	183	15.665	27.264	9.599	1.00	53.61	N
ATOM	1447	N	ASP	A	184	11.319	29.655	13.142	1.00	48.66	N
ATOM	1448	CA	ASP	A	184	10.797	28.751	14.156	1.00	52.92	C
ATOM	1449	C	ASP	A	184	11.722	27.567	14.333	1.00	45.71	C
ATOM	1450	O	ASP	A	184	12.104	26.894	13.371	1.00	44.54	O
ATOM	1451	CB	ASP	A	184	9.404	28.255	13.784	1.00	62.54	C
ATOM	1452	CG	ASP	A	184	8.338	29.306	14.007	1.00	62.50	C
ATOM	1453	OD1	ASP	A	184	8.407	30.010	15.038	1.00	56.56	O
ATOM	1454	OD2	ASP	A	184	7.429	29.417	13.155	1.00	70.30	O
ATOM	1455	N	ILE	A	185	12.085	27.313	15.576	1.00	40.93	N
ATOM	1456	CA	ILE	A	185	12.993	26.219	15.849	1.00	39.71	C
ATOM	1457	C	ILE	A	185	12.372	25.231	16.806	1.00	38.52	C
ATOM	1458	O	ILE	A	185	11.958	25.590	17.909	1.00	38.65	O
ATOM	1459	CB	ILE	A	185	14.326	26.752	16.417	1.00	41.45	C
ATOM	1460	CG1	ILE	A	185	15.051	27.548	15.316	1.00	46.89	C
ATOM	1461	CG2	ILE	A	185	15.199	25.580	16.922	1.00	37.86	C
ATOM	1462	CD1	ILE	A	185	16.246	28.337	15.805	1.00	48.29	C
ATOM	1463	N	GLN	A	186	12.291	23.984	16.355	1.00	42.25	N
ATOM	1464	CA	GLN	A	186	11.744	22.916	17.181	1.00	41.47	C
ATOM	1465	C	GLN	A	186	12.857	22.416	18.097	1.00	38.63	C
ATOM	1466	O	GLN	A	186	13.916	21.991	17.630	1.00	42.48	O
ATOM	1467	CB	GLN	A	186	11.247	21.755	16.307	1.00	52.01	C
ATOM	1468	CG	GLN	A	186	10.732	20.542	17.100	1.00	64.38	C
ATOM	1469	CD	GLN	A	186	10.353	19.348	16.204	1.00	79.51	C
ATOM	1470	OE1	GLN	A	186	10.873	19.202	15.092	1.00	79.17	O
ATOM	1471	NE2	GLN	A	186	9.465	18.481	16.701	1.00	80.31	N
ATOM	1472	N	VAL	A	187	12.610	22.457	19.398	1.00	43.44	N
ATOM	1473	CA	VAL	A	187	13.586	21.987	20.367	1.00	47.67	C
ATOM	1474	C	VAL	A	187	13.146	20.607	20.866	1.00	49.13	C
ATOM	1475	O	VAL	A	187	12.015	20.446	21.311	1.00	40.93	O
ATOM	1476	CB	VAL	A	187	13.675	22.939	21.583	1.00	42.03	C
ATOM	1477	CG1	VAL	A	187	14.563	22.315	22.652	1.00	41.16	C
ATOM	1478	CG2	VAL	A	187	14.224	24.300	21.154	1.00	38.03	C
ATOM	1479	N	ILE	A	188	14.035	19.621	20.785	1.00	41.32	N
ATOM	1480	CA	ILE	A	188	13.733	18.273	21.255	1.00	42.62	C
ATOM	1481	C	ILE	A	188	14.635	17.913	22.441	1.00	40.36	C
ATOM	1482	O	ILE	A	188	15.835	18.224	22.442	1.00	42.29	O
ATOM	1483	CB	ILE	A	188	13.945	17.213	20.142	1.00	45.03	C
ATOM	1484	CG1	ILE	A	188	13.002	17.475	18.967	1.00	41.79	C

ATOM	1485	CG2	ILE	A	188	13.687	15.806	20.702	1.00	46.59	C
ATOM	1486	CD1	ILE	A	188	13.267	16.566	17.763	1.00	40.92	C
ATOM	1487	N	VAL	A	189	14.050	17.285	23.455	1.00	36.36	N
ATOM	1488	CA	VAL	A	189	14.808	16.867	24.627	1.00	42.50	C
ATOM	1489	C	VAL	A	189	14.802	15.338	24.667	1.00	48.22	C
ATOM	1490	O	VAL	A	189	13.748	14.705	24.672	1.00	41.17	O
ATOM	1491	CB	VAL	A	189	14.206	17.455	25.921	1.00	44.30	C
ATOM	1492	CG1	VAL	A	189	14.945	16.930	27.125	1.00	39.49	C
ATOM	1493	CG2	VAL	A	189	14.304	18.966	25.894	1.00	40.56	C
ATOM	1494	N	ASN	A	190	15.993	14.754	24.665	1.00	40.63	N
ATOM	1495	CA	ASN	A	190	16.143	13.316	24.698	1.00	40.98	C
ATOM	1496	C	ASN	A	190	16.395	12.885	26.148	1.00	45.73	C
ATOM	1497	O	ASN	A	190	17.018	13.613	26.918	1.00	45.44	O
ATOM	1498	CB	ASN	A	190	17.285	12.908	23.752	1.00	40.78	C
ATOM	1499	CG	ASN	A	190	16.999	13.293	22.310	1.00	48.31	C
ATOM	1500	OD1	ASN	A	190	15.917	13.005	21.782	1.00	44.75	O
ATOM	1501	ND2	ASN	A	190	17.962	13.951	21.664	1.00	41.66	N
ATOM	1502	N	VAL	A	191	15.877	11.710	26.509	1.00	42.84	N
ATOM	1503	CA	VAL	A	191	15.982	11.151	27.863	1.00	39.39	C
ATOM	1504	C	VAL	A	191	16.683	9.802	27.788	1.00	39.64	C
ATOM	1505	O	VAL	A	191	16.261	8.910	27.043	1.00	47.40	O
ATOM	1506	CB	VAL	A	191	14.574	10.954	28.470	1.00	44.63	C
ATOM	1507	CG1	VAL	A	191	14.671	10.368	29.890	1.00	41.78	C
ATOM	1508	CG2	VAL	A	191	13.848	12.310	28.499	1.00	41.72	C
ATOM	1509	N	PRO	A	192	17.775	9.641	28.542	1.00	43.27	N
ATOM	1510	CA	PRO	A	192	18.578	8.416	28.596	1.00	45.21	C
ATOM	1511	C	PRO	A	192	17.722	7.224	28.990	1.00	42.00	C
ATOM	1512	O	PRO	A	192	16.783	7.355	29.763	1.00	42.35	O
ATOM	1513	CB	PRO	A	192	19.620	8.737	29.668	1.00	49.92	C
ATOM	1514	CG	PRO	A	192	19.690	10.204	29.687	1.00	49.81	C
ATOM	1515	CD	PRO	A	192	18.246	10.602	29.556	1.00	43.30	C
ATOM	1516	N	PRO	A	193	18.075	6.034	28.515	1.00	40.57	N
ATOM	1517	CA	PRO	A	193	17.301	4.848	28.838	1.00	39.79	C
ATOM	1518	C	PRO	A	193	17.516	4.372	30.256	1.00	43.45	C
ATOM	1519	O	PRO	A	193	18.552	4.666	30.864	1.00	44.20	O
ATOM	1520	CB	PRO	A	193	17.842	3.809	27.853	1.00	41.07	C
ATOM	1521	CG	PRO	A	193	18.661	4.630	26.843	1.00	46.01	C
ATOM	1522	CD	PRO	A	193	19.250	5.657	27.729	1.00	47.13	C
ATOM	1523	N	THR	A	194	16.516	3.665	30.779	1.00	45.04	N
ATOM	1524	CA	THR	A	194	16.614	2.987	32.075	1.00	48.33	C
ATOM	1525	C	THR	A	194	16.019	1.623	31.713	1.00	51.40	C
ATOM	1526	O	THR	A	194	15.124	1.529	30.848	1.00	41.84	O
ATOM	1527	CB	THR	A	194	15.792	3.630	33.225	1.00	48.61	C
ATOM	1528	OG1	THR	A	194	14.414	3.724	32.862	1.00	54.30	O
ATOM	1529	CG2	THR	A	194	16.338	4.992	33.574	1.00	57.24	C
ATOM	1530	N	VAL	A	195	16.507	0.565	32.352	1.00	48.50	N
ATOM	1531	CA	VAL	A	195	16.026	-0.760	32.017	1.00	45.60	C
ATOM	1532	C	VAL	A	195	16.083	-1.715	33.200	1.00	42.61	C
ATOM	1533	O	VAL	A	195	16.976	-1.644	34.021	1.00	46.25	O
ATOM	1534	CB	VAL	A	195	16.853	-1.346	30.840	1.00	42.93	C
ATOM	1535	CG1	VAL	A	195	18.314	-1.582	31.282	1.00	43.08	C
ATOM	1536	CG2	VAL	A	195	16.218	-2.635	30.339	1.00	43.46	C
ATOM	1537	N	GLN	A	196	15.104	-2.603	33.282	1.00	41.51	N
ATOM	1538	CA	GLN	A	196	15.070	-3.577	34.355	1.00	48.63	C
ATOM	1539	C	GLN	A	196	14.615	-4.928	33.817	1.00	46.66	C
ATOM	1540	O	GLN	A	196	13.706	-5.009	32.992	1.00	45.71	O
ATOM	1541	CB	GLN	A	196	14.119	-3.118	35.477	1.00	49.59	C
ATOM	1542	CG	GLN	A	196	14.693	-2.064	36.393	1.00	55.69	C
ATOM	1543	CD	GLN	A	196	13.790	-1.757	37.588	1.00	74.35	C

ATOM	1544	OE1	GLN	A	196	14.268	-1.328	38.639	1.00	74.51	O
ATOM	1545	NE2	GLN	A	196	12.482	-1.970	37.429	1.00	79.78	N
ATOM	1546	N	ALA	A	197	15.257	-5.991	34.282	1.00	40.70	N
ATOM	1547	CA	ALA	A	197	14.876	-7.329	33.873	1.00	39.75	C
ATOM	1548	C	ALA	A	197	13.550	-7.650	34.550	1.00	42.61	C
ATOM	1549	O	ALA	A	197	13.316	-7.246	35.687	1.00	48.54	O
ATOM	1550	CB	ALA	A	197	15.940	-8.333	34.313	1.00	39.72	C
ATOM	1551	N	ARG	A	198	12.671	-8.368	33.865	1.00	43.54	N
ATOM	1552	CA	ARG	A	198	11.403	-8.720	34.485	1.00	44.25	C
ATOM	1553	C	ARG	A	198	11.664	-9.866	35.479	1.00	53.02	C
ATOM	1554	O	ARG	A	198	11.018	-9.960	36.528	1.00	45.60	O
ATOM	1555	CB	ARG	A	198	10.392	-9.131	33.416	1.00	49.38	C
ATOM	1556	CG	ARG	A	198	8.967	-8.992	33.873	1.00	56.08	C
ATOM	1557	CD	ARG	A	198	7.991	-9.099	32.724	1.00	58.30	C
ATOM	1558	NE	ARG	A	198	7.873	-7.869	31.947	1.00	47.20	N
ATOM	1559	CZ	ARG	A	198	6.931	-7.675	31.030	1.00	54.23	C
ATOM	1560	NH1	ARG	A	198	6.038	-8.633	30.793	1.00	47.47	N
ATOM	1561	NH2	ARG	A	198	6.882	-6.541	30.339	1.00	50.85	N
ATOM	1562	N	GLN	A	199	12.625	-10.722	35.133	1.00	51.86	N
ATOM	1563	CA	GLN	A	199	13.047	-11.844	35.965	1.00	52.79	C
ATOM	1564	C	GLN	A	199	14.564	-11.926	35.871	1.00	50.17	C
ATOM	1565	O	GLN	A	199	15.107	-12.162	34.798	1.00	54.53	O
ATOM	1566	CB	GLN	A	199	12.447	-13.159	35.472	1.00	58.34	C
ATOM	1567	CG	GLN	A	199	10.941	-13.292	35.635	1.00	68.50	C
ATOM	1568	CD	GLN	A	199	10.498	-13.315	37.100	1.00	83.24	C
ATOM	1569	OE1	GLN	A	199	11.300	-13.596	37.996	1.00	85.74	O
ATOM	1570	NE2	GLN	A	199	9.214	-13.035	37.347	1.00	71.40	N
ATOM	1571	N	SER	A	200	15.247	-11.719	36.991	1.00	46.12	N
ATOM	1572	CA	SER	A	200	16.715	-11.753	37.042	1.00	50.15	C
ATOM	1573	C	SER	A	200	17.328	-13.157	37.004	1.00	47.60	C
ATOM	1574	O	SER	A	200	18.458	-13.350	36.541	1.00	49.49	O
ATOM	1575	CB	SER	A	200	17.194	-11.061	38.318	1.00	49.46	C
ATOM	1576	OG	SER	A	200	16.702	-9.737	38.384	1.00	76.11	O
ATOM	1577	N	ILE	A	201	16.576	-14.122	37.518	1.00	48.87	N
ATOM	1578	CA	ILE	A	201	17.019	-15.504	37.591	1.00	50.62	C
ATOM	1579	C	ILE	A	201	15.994	-16.400	36.925	1.00	47.35	C
ATOM	1580	O	ILE	A	201	14.797	-16.328	37.216	1.00	51.41	O
ATOM	1581	CB	ILE	A	201	17.181	-15.962	39.067	1.00	64.29	C
ATOM	1582	CG1	ILE	A	201	18.080	-14.983	39.838	1.00	57.76	C
ATOM	1583	CG2	ILE	A	201	17.768	-17.373	39.116	1.00	58.42	C
ATOM	1584	CD1	ILE	A	201	19.476	-14.860	39.290	1.00	68.87	C
ATOM	1585	N	VAL	A	202	16.469	-17.249	36.032	1.00	46.21	N
ATOM	1586	CA	VAL	A	202	15.587	-18.157	35.339	1.00	49.25	C
ATOM	1587	C	VAL	A	202	16.207	-19.540	35.336	1.00	47.17	C
ATOM	1588	O	VAL	A	202	17.391	-19.687	35.045	1.00	43.79	O
ATOM	1589	CB	VAL	A	202	15.371	-17.701	33.882	1.00	53.12	C
ATOM	1590	CG1	VAL	A	202	14.436	-18.661	33.177	1.00	45.19	C
ATOM	1591	CG2	VAL	A	202	14.820	-16.276	33.861	1.00	50.64	C
ATOM	1592	N	ASN	A	203	15.393	-20.544	35.653	1.00	49.57	N
ATOM	1593	CA	ASN	A	203	15.827	-21.937	35.680	1.00	51.28	C
ATOM	1594	C	ASN	A	203	15.078	-22.676	34.575	1.00	55.81	C
ATOM	1595	O	ASN	A	203	13.857	-22.541	34.440	1.00	50.57	O
ATOM	1596	CB	ASN	A	203	15.473	-22.635	37.010	1.00	49.03	C
ATOM	1597	CG	ASN	A	203	16.218	-22.067	38.217	1.00	47.83	C
ATOM	1598	OD1	ASN	A	203	17.319	-21.530	38.105	1.00	47.54	O
ATOM	1599	ND2	ASN	A	203	15.617	-22.217	39.390	1.00	44.22	N
ATOM	1600	N	ALA	A	204	15.811	-23.487	33.825	1.00	53.79	N
ATOM	1601	CA	ALA	A	204	15.249	-24.272	32.738	1.00	58.78	C
ATOM	1602	C	ALA	A	204	15.827	-25.683	32.730	1.00	59.86	C

ATOM	1603	O	ALA	A	204	16.909	-25.933	33.268	1.00	58.63	O
ATOM	1604	CB	ALA	A	204	15.541	-23.592	31.408	1.00	54.08	C
ATOM	1605	N	THR	A	205	15.088	-26.592	32.100	1.00	63.01	N
ATOM	1606	CA	THR	A	205	15.483	-27.989	31.966	1.00	62.26	C
ATOM	1607	C	THR	A	205	15.949	-28.248	30.546	1.00	59.60	C
ATOM	1608	O	THR	A	205	15.282	-27.874	29.579	1.00	57.70	O
ATOM	1609	CB	THR	A	205	14.323	-28.946	32.265	1.00	63.31	C
ATOM	1610	OG1	THR	A	205	13.916	-28.799	33.634	1.00	64.86	O
ATOM	1611	CG2	THR	A	205	14.760	-30.383	32.012	1.00	70.94	C
ATOM	1612	N	ALA	A	206	17.089	-28.913	30.430	1.00	56.34	N
ATOM	1613	CA	ALA	A	206	17.670	-29.203	29.134	1.00	60.33	C
ATOM	1614	C	ALA	A	206	17.035	-30.352	28.375	1.00	64.54	C
ATOM	1615	O	ALA	A	206	16.377	-31.228	28.940	1.00	68.98	O
ATOM	1616	CB	ALA	A	206	19.156	-29.464	29.290	1.00	58.07	C
ATOM	1617	N	ASN	A	207	17.246	-30.306	27.067	1.00	71.10	N
ATOM	1618	CA	ASN	A	207	16.791	-31.322	26.140	1.00	71.82	C
ATOM	1619	C	ASN	A	207	15.352	-31.788	26.216	1.00	70.92	C
ATOM	1620	O	ASN	A	207	15.077	-32.971	26.023	1.00	73.91	O
ATOM	1621	CB	ASN	A	207	17.724	-32.518	26.249	1.00	69.97	C
ATOM	1622	CG	ASN	A	207	19.170	-32.119	26.105	1.00	75.29	C
ATOM	1623	OD1	ASN	A	207	19.562	-31.531	25.097	1.00	81.94	O
ATOM	1624	ND2	ASN	A	207	19.972	-32.421	27.115	1.00	80.72	N
ATOM	1625	N	LEU	A	208	14.432	-30.877	26.496	1.00	67.07	N
ATOM	1626	CA	LEU	A	208	13.026	-31.246	26.528	1.00	68.52	C
ATOM	1627	C	LEU	A	208	12.347	-30.484	25.391	1.00	67.74	C
ATOM	1628	O	LEU	A	208	11.122	-30.415	25.306	1.00	73.14	O
ATOM	1629	CB	LEU	A	208	12.393	-30.904	27.877	1.00	68.09	C
ATOM	1630	CG	LEU	A	208	12.930	-31.679	29.091	1.00	79.90	C
ATOM	1631	CD1	LEU	A	208	12.105	-31.321	30.319	1.00	73.01	C
ATOM	1632	CD2	LEU	A	208	12.854	-33.180	28.843	1.00	77.54	C
ATOM	1633	N	GLY	A	209	13.175	-29.907	24.519	1.00	74.00	N
ATOM	1634	CA	GLY	A	209	12.694	-29.159	23.364	1.00	81.72	C
ATOM	1635	C	GLY	A	209	11.907	-27.893	23.667	1.00	87.49	C
ATOM	1636	O	GLY	A	209	11.241	-27.341	22.788	1.00	95.12	O
ATOM	1637	N	GLN	A	210	11.992	-27.420	24.905	1.00	84.00	N
ATOM	1638	CA	GLN	A	210	11.254	-26.230	25.299	1.00	82.13	C
ATOM	1639	C	GLN	A	210	12.033	-24.922	25.205	1.00	74.00	C
ATOM	1640	O	GLN	A	210	13.265	-24.922	25.132	1.00	71.75	O
ATOM	1641	CB	GLN	A	210	10.703	-26.400	26.711	1.00	86.64	C
ATOM	1642	CG	GLN	A	210	11.770	-26.685	27.754	1.00	92.84	C
ATOM	1643	CD	GLN	A	210	11.215	-27.469	28.932	1.00	98.28	C
ATOM	1644	OE1	GLN	A	210	10.047	-27.856	28.930	1.00	102.57	O
ATOM	1645	NE2	GLN	A	210	12.049	-27.714	29.938	1.00	100.49	N
ATOM	1646	N	SER	A	211	11.295	-23.810	25.212	1.00	73.42	N
ATOM	1647	CA	SER	A	211	11.873	-22.470	25.101	1.00	68.89	C
ATOM	1648	C	SER	A	211	11.749	-21.688	26.394	1.00	59.63	C
ATOM	1649	O	SER	A	211	10.995	-22.044	27.297	1.00	58.00	O
ATOM	1650	CB	SER	A	211	11.181	-21.680	23.978	1.00	69.06	C
ATOM	1651	OG	SER	A	211	11.312	-22.319	22.719	1.00	75.29	O
ATOM	1652	N	VAL	A	212	12.515	-20.616	26.479	1.00	62.83	N
ATOM	1653	CA	VAL	A	212	12.470	-19.749	27.638	1.00	57.69	C
ATOM	1654	C	VAL	A	212	12.482	-18.343	27.056	1.00	51.71	C
ATOM	1655	O	VAL	A	212	13.140	-18.086	26.044	1.00	48.36	O
ATOM	1656	CB	VAL	A	212	13.697	-19.965	28.554	1.00	58.76	C
ATOM	1657	CG1	VAL	A	212	14.970	-19.802	27.762	1.00	57.99	C
ATOM	1658	CG2	VAL	A	212	13.665	-18.988	29.707	1.00	65.40	C
ATOM	1659	N	THR	A	213	11.738	-17.438	27.672	1.00	48.53	N
ATOM	1660	CA	THR	A	213	11.698	-16.079	27.171	1.00	50.94	C
ATOM	1661	C	THR	A	213	12.279	-15.100	28.194	1.00	46.89	C

Table 2

ATOM	1662	O	THR	A	213	11.760	-14.969	29.301	1.00	48.85 O
ATOM	1663	CB	THR	A	213	10.246	-15.669	26.820	1.00	50.59 C
ATOM	1664	OG1	THR	A	213	9.720	-16.556	25.827	1.00	54.06 O
ATOM	1665	CG2	THR	A	213	10.214	-14.255	26.276	1.00	56.06 C
ATOM	1666	N	LEU	A	214	13.367	-14.430	27.823	1.00	50.67 N
ATOM	1667	CA	LEU	A	214	14.015	-13.445	28.686	1.00	44.75 C
ATOM	1668	C	LEU	A	214	13.444	-12.078	28.327	1.00	49.46 C
ATOM	1669	O	LEU	A	214	13.339	-11.738	27.147	1.00	40.16 O
ATOM	1670	CB	LEU	A	214	15.519	-13.469	28.464	1.00	40.05 C
ATOM	1671	CG	LEU	A	214	16.140	-14.857	28.611	1.00	47.06 C
ATOM	1672	CD1	LEU	A	214	17.647	-14.728	28.666	1.00	41.62 C
ATOM	1673	CD2	LEU	A	214	15.623	-15.532	29.880	1.00	42.47 C
ATOM	1674	N	VAL	A	215	13.089	-11.299	29.345	1.00	44.86 N
ATOM	1675	CA	VAL	A	215	12.454	-10.004	29.143	1.00	46.92 C
ATOM	1676	C	VAL	A	215	13.030	-8.850	29.928	1.00	48.90 C
ATOM	1677	O	VAL	A	215	13.254	-8.937	31.135	1.00	50.91 O
ATOM	1678	CB	VAL	A	215	10.969	-10.089	29.508	1.00	49.64 C
ATOM	1679	CG1	VAL	A	215	10.265	-8.759	29.213	1.00	50.90 C
ATOM	1680	CG2	VAL	A	215	10.332	-11.234	28.765	1.00	52.37 C
ATOM	1681	N	CYS	A	216	13.254	-7.755	29.221	1.00	44.39 N
ATOM	1682	CA	CYS	A	216	13.754	-6.542	29.826	1.00	45.29 C
ATOM	1683	C	CYS	A	216	12.744	-5.449	29.501	1.00	52.26 C
ATOM	1684	O	CYS	A	216	12.223	-5.399	28.393	1.00	47.28 O
ATOM	1685	CB	CYS	A	216	15.122	-6.180	29.257	1.00	45.92 C
ATOM	1686	SG	CYS	A	216	16.483	-7.140	29.998	1.00	51.48 S
ATOM	1687	N	ASP	A	217	12.454	-4.598	30.478	1.00	44.49 N
ATOM	1688	CA	ASP	A	217	11.523	-3.499	30.291	1.00	46.18 C
ATOM	1689	C	ASP	A	217	12.330	-2.230	30.313	1.00	46.02 C
ATOM	1690	O	ASP	A	217	12.974	-1.906	31.307	1.00	42.34 O
ATOM	1691	CB	ASP	A	217	10.501	-3.453	31.419	1.00	43.07 C
ATOM	1692	CG	ASP	A	217	9.576	-4.624	31.382	1.00	54.67 C
ATOM	1693	OD1	ASP	A	217	8.860	-4.755	30.366	1.00	54.44 O
ATOM	1694	OD2	ASP	A	217	9.573	-5.417	32.350	1.00	52.78 O
ATOM	1695	N	ALA	A	218	12.279	-1.498	29.215	1.00	43.43 N
ATOM	1696	CA	ALA	A	218	13.030	-0.269	29.129	1.00	51.56 C
ATOM	1697	C	ALA	A	218	12.205	0.900	28.633	1.00	51.78 C
ATOM	1698	O	ALA	A	218	11.150	0.731	28.031	1.00	48.04 O
ATOM	1699	CB	ALA	A	218	14.221	-0.468	28.202	1.00	46.61 C
ATOM	1700	N	ASP	A	219	12.704	2.096	28.901	1.00	47.98 N
ATOM	1701	CA	ASP	A	219	12.076	3.287	28.377	1.00	53.40 C
ATOM	1702	C	ASP	A	219	13.097	4.412	28.287	1.00	54.39 C
ATOM	1703	O	ASP	A	219	14.214	4.308	28.791	1.00	53.10 O
ATOM	1704	CB	ASP	A	219	10.876	3.693	29.214	1.00	67.27 C
ATOM	1705	CG	ASP	A	219	11.226	3.878	30.644	1.00	73.00 C
ATOM	1706	OD1	ASP	A	219	12.424	4.087	30.905	1.00	77.65 O
ATOM	1707	OD2	ASP	A	219	10.315	3.824	31.502	1.00	83.21 O
ATOM	1708	N	GLY	A	220	12.693	5.482	27.622	1.00	46.12 N
ATOM	1709	CA	GLY	A	220	13.541	6.632	27.405	1.00	43.59 C
ATOM	1710	C	GLY	A	220	13.035	7.266	26.135	1.00	46.49 C
ATOM	1711	O	GLY	A	220	12.062	6.810	25.554	1.00	45.48 O
ATOM	1712	N	PHE	A	221	13.700	8.341	25.678	1.00	43.50 N
ATOM	1713	CA	PHE	A	221	13.283	9.017	24.465	1.00	42.29 C
ATOM	1714	C	PHE	A	221	14.499	9.499	23.669	1.00	33.90 C
ATOM	1715	O	PHE	A	221	15.313	10.265	24.178	1.00	43.58 O
ATOM	1716	CB	PHE	A	221	12.391	10.215	24.797	1.00	41.04 C
ATOM	1717	CG	PHE	A	221	11.792	10.861	23.572	1.00	44.52 C
ATOM	1718	CD1	PHE	A	221	10.591	10.395	23.037	1.00	47.33 C
ATOM	1719	CD2	PHE	A	221	12.482	11.863	22.891	1.00	44.34 C
ATOM	1720	CE1	PHE	A	221	10.088	10.910	21.837	1.00	45.26 C

Table 2

ATOM	1721	CE2	PHE	A	221	11.989	12.380	21.693	1.00	48.97 C
ATOM	1722	CZ	PHE	A	221	10.785	11.897	21.166	1.00	44.61 C
ATOM	1723	N	PRO	A	222	14.645	9.050	22.400	1.00	40.11 N
ATOM	1724	CA	PRO	A	222	13.780	8.122	21.655	1.00	40.06 C
ATOM	1725	C	PRO	A	222	13.693	6.765	22.344	1.00	50.45 C
ATOM	1726	O	PRO	A	222	14.546	6.419	23.172	1.00	43.37 O
ATOM	1727	CB	PRO	A	222	14.480	8.000	20.307	1.00	44.90 C
ATOM	1728	CG	PRO	A	222	15.163	9.311	20.158	1.00	43.89 C
ATOM	1729	CD	PRO	A	222	15.733	9.547	21.536	1.00	38.16 C
ATOM	1730	N	GLU	A	223	12.659	5.999	21.998	1.00	47.32 N
ATOM	1731	CA	GLU	A	223	12.466	4.664	22.565	1.00	48.48 C
ATOM	1732	C	GLU	A	223	13.778	3.917	22.403	1.00	44.89 C
ATOM	1733	O	GLU	A	223	14.364	3.886	21.321	1.00	42.04 O
ATOM	1734	CB	GLU	A	223	11.359	3.905	21.837	1.00	51.24 C
ATOM	1735	CG	GLU	A	223	9.947	4.402	22.100	1.00	45.06 C
ATOM	1736	CD	GLU	A	223	9.513	4.303	23.556	1.00	60.54 C
ATOM	1737	OE1	GLU	A	223	9.950	3.368	24.263	1.00	71.83 O
ATOM	1738	OE2	GLU	A	223	8.700	5.153	23.986	1.00	70.97 O
ATOM	1739	N	PRO	A	224	14.249	3.296	23.483	1.00	46.34 N
ATOM	1740	CA	PRO	A	224	15.507	2.559	23.453	1.00	48.92 C
ATOM	1741	C	PRO	A	224	15.536	1.373	22.501	1.00	49.30 C
ATOM	1742	O	PRO	A	224	14.535	0.692	22.311	1.00	47.42 O
ATOM	1743	CB	PRO	A	224	15.678	2.113	24.911	1.00	47.68 C
ATOM	1744	CG	PRO	A	224	14.893	3.128	25.698	1.00	57.81 C
ATOM	1745	CD	PRO	A	224	13.673	3.314	24.843	1.00	47.48 C
ATOM	1746	N	THR	A	225	16.685	1.143	21.884	1.00	50.13 N
ATOM	1747	CA	THR	A	225	16.859	-0.016	21.021	1.00	60.61 C
ATOM	1748	C	THR	A	225	17.598	-1.033	21.907	1.00	59.15 C
ATOM	1749	O	THR	A	225	18.533	-0.663	22.631	1.00	47.10 O
ATOM	1750	CB	THR	A	225	17.723	0.319	19.810	1.00	58.08 C
ATOM	1751	OG1	THR	A	225	17.027	1.259	18.985	1.00	83.82 O
ATOM	1752	CG2	THR	A	225	18.009	-0.934	19.003	1.00	73.24 C
ATOM	1753	N	MET	A	226	17.189	-2.296	21.862	1.00	52.21 N
ATOM	1754	CA	MET	A	226	17.824	-3.310	22.692	1.00	53.46 C
ATOM	1755	C	MET	A	226	18.721	-4.265	21.927	1.00	56.38 C
ATOM	1756	O	MET	A	226	18.417	-4.657	20.802	1.00	51.69 O
ATOM	1757	CB	MET	A	226	16.766	-4.149	23.397	1.00	61.02 C
ATOM	1758	CG	MET	A	226	15.711	-3.339	24.112	1.00	73.13 C
ATOM	1759	SD	MET	A	226	16.515	-2.409	25.388	1.00	79.72 S
ATOM	1760	CE	MET	A	226	17.052	-3.791	26.474	1.00	72.80 C
ATOM	1761	N	SER	A	227	19.821	-4.649	22.564	1.00	51.74 N
ATOM	1762	CA	SER	A	227	20.755	-5.617	22.003	1.00	57.86 C
ATOM	1763	C	SER	A	227	21.169	-6.496	23.187	1.00	61.93 C
ATOM	1764	O	SER	A	227	21.204	-6.024	24.332	1.00	60.05 O
ATOM	1765	CB	SER	A	227	21.961	-4.912	21.403	1.00	41.57 C
ATOM	1766	OG	SER	A	227	22.546	-4.056	22.355	1.00	62.88 O
ATOM	1767	N	TRP	A	228	21.472	-7.765	22.924	1.00	57.15 N
ATOM	1768	CA	TRP	A	228	21.840	-8.689	23.998	1.00	55.47 C
ATOM	1769	C	TRP	A	228	23.243	-9.290	23.899	1.00	59.04 C
ATOM	1770	O	TRP	A	228	23.856	-9.273	22.829	1.00	49.40 O
ATOM	1771	CB	TRP	A	228	20.842	-9.840	24.050	1.00	49.35 C
ATOM	1772	CG	TRP	A	228	19.435	-9.439	24.308	1.00	47.96 C
ATOM	1773	CD1	TRP	A	228	18.630	-8.695	23.494	1.00	53.38 C
ATOM	1774	CD2	TRP	A	228	18.654	-9.760	25.462	1.00	47.76 C
ATOM	1775	NE1	TRP	A	228	17.394	-8.537	24.067	1.00	52.08 N
ATOM	1776	CE2	TRP	A	228	17.379	-9.177	25.279	1.00	45.77 C
ATOM	1777	CE3	TRP	A	228	18.906	-10.482	26.637	1.00	42.71 C
ATOM	1778	CZ2	TRP	A	228	16.355	-9.291	26.227	1.00	37.55 C
ATOM	1779	CZ3	TRP	A	228	17.887	-10.598	27.586	1.00	45.83 C

ATOM	1780	CH2	TRP	A	228	16.625	-10.004	27.373	1.00	50.85 C
ATOM	1781	N	THR	A	229	23.749	-9.795	25.027	1.00	58.07 N
ATOM	1782	CA	THR	A	229	25.047	-10.474	25.057	1.00	60.10 C
ATOM	1783	C	THR	A	229	24.918	-11.741	25.902	1.00	61.83 C
ATOM	1784	O	THR	A	229	24.132	-11.787	26.868	1.00	54.86 O
ATOM	1785	CB	THR	A	229	26.191	-9.610	25.652	1.00	53.98 C
ATOM	1786	OG1	THR	A	229	25.882	-9.252	26.999	1.00	57.01 O
ATOM	1787	CG2	THR	A	229	26.418	-8.373	24.816	1.00	57.89 C
ATOM	1788	N	LYS	A	230	25.677	-12.765	25.515	1.00	58.82 N
ATOM	1789	CA	LYS	A	230	25.684	-14.043	26.217	1.00	58.37 C
ATOM	1790	C	LYS	A	230	27.088	-14.147	26.792	1.00	52.83 C
ATOM	1791	O	LYS	A	230	28.066	-14.266	26.054	1.00	54.49 O
ATOM	1792	CB	LYS	A	230	25.396	-15.173	25.227	1.00	55.01 C
ATOM	1793	CG	LYS	A	230	25.113	-16.539	25.849	1.00	45.56 C
ATOM	1794	CD	LYS	A	230	24.973	-17.615	24.757	1.00	59.41 C
ATOM	1795	CE	LYS	A	230	24.803	-19.019	25.339	1.00	62.34 C
ATOM	1796	NZ	LYS	A	230	24.460	-20.050	24.304	1.00	59.23 N
ATOM	1797	N	ASP	A	231	27.183	-14.078	28.115	1.00	61.62 N
ATOM	1798	CA	ASP	A	231	28.479	-14.105	28.781	1.00	69.33 C
ATOM	1799	C	ASP	A	231	29.439	-13.118	28.113	1.00	69.66 C
ATOM	1800	O	ASP	A	231	30.612	-13.429	27.916	1.00	73.37 O
ATOM	1801	CB	ASP	A	231	29.096	-15.509	28.754	1.00	67.95 C
ATOM	1802	CG	ASP	A	231	28.359	-16.492	29.645	1.00	76.63 C
ATOM	1803	OD1	ASP	A	231	27.830	-16.069	30.697	1.00	73.37 O
ATOM	1804	OD2	ASP	A	231	28.327	-17.692	29.295	1.00	73.07 O
ATOM	1805	N	GLY	A	232	28.939	-11.933	27.766	1.00	69.81 N
ATOM	1806	CA	GLY	A	232	29.780	-10.925	27.147	1.00	62.92 C
ATOM	1807	C	GLY	A	232	29.815	-10.953	25.633	1.00	57.21 C
ATOM	1808	O	GLY	A	232	30.217	-9.985	24.999	1.00	64.11 O
ATOM	1809	N	GLU	A	233	29.398	-12.058	25.039	1.00	60.24 N
ATOM	1810	CA	GLU	A	233	29.407	-12.163	23.587	1.00	67.77 C
ATOM	1811	C	GLU	A	233	28.086	-11.753	22.977	1.00	69.76 C
ATOM	1812	O	GLU	A	233	27.019	-12.146	23.437	1.00	67.85 O
ATOM	1813	CB	GLU	A	233	29.721	-13.589	23.156	1.00	73.47 C
ATOM	1814	CG	GLU	A	233	31.174	-13.980	23.298	1.00	93.05 C
ATOM	1815	CD	GLU	A	233	32.100	-13.154	22.416	1.00	101.69 C
ATOM	1816	OE1	GLU	A	233	31.753	-12.894	21.241	1.00	104.10 O
ATOM	1817	OE2	GLU	A	233	33.189	-12.771	22.898	1.00	105.15 O
ATOM	1818	N	PRO	A	234	28.146	-10.986	21.894	1.00	69.71 N
ATOM	1819	CA	PRO	A	234	26.928	-10.527	21.227	1.00	69.07 C
ATOM	1820	C	PRO	A	234	26.042	-11.660	20.747	1.00	63.95 C
ATOM	1821	O	PRO	A	234	26.516	-12.774	20.513	1.00	68.33 O
ATOM	1822	CB	PRO	A	234	27.463	-9.717	20.047	1.00	74.23 C
ATOM	1823	CG	PRO	A	234	28.863	-9.346	20.458	1.00	78.24 C
ATOM	1824	CD	PRO	A	234	29.349	-10.575	21.151	1.00	73.22 C
ATOM	1825	N	ILE	A	235	24.756	-11.361	20.589	1.00	60.42 N
ATOM	1826	CA	ILE	A	235	23.819	-12.347	20.075	1.00	59.30 C
ATOM	1827	C	ILE	A	235	23.091	-11.707	18.887	1.00	73.94 C
ATOM	1828	O	ILE	A	235	22.292	-10.780	19.062	1.00	69.18 O
ATOM	1829	CB	ILE	A	235	22.785	-12.748	21.118	1.00	58.75 C
ATOM	1830	CG1	ILE	A	235	23.480	-13.103	22.435	1.00	60.61 C
ATOM	1831	CG2	ILE	A	235	21.986	-13.935	20.602	1.00	54.52 C
ATOM	1832	CD1	ILE	A	235	22.535	-13.237	23.598	1.00	58.31 C
ATOM	1833	N	GLU	A	236	23.341	-12.205	17.679	1.00	80.94 N
ATOM	1834	CA	GLU	A	236	22.742	-11.605	16.488	1.00	90.13 C
ATOM	1835	C	GLU	A	236	21.234	-11.755	16.308	1.00	93.13 C
ATOM	1836	O	GLU	A	236	20.685	-12.857	16.339	1.00	89.58 O
ATOM	1837	CB	GLU	A	236	23.493	-12.094	15.252	1.00	98.19 C
ATOM	1838	CC	GLU	A	236	25.017	-12.039	15.429	1.00	107.77 C

ATOM	1839	CD	GLU	A	236	25.542	-10.662	15.844	1.00	115.02 C
ATOM	1840	OE1	GLU	A	236	24.988	-10.055	16.788	1.00	121.81 O
ATOM	1841	OE2	GLU	A	236	26.526	-10.191	15.233	1.00	116.63 O
ATOM	1842	N	ASN	A	237	20.585	-10.606	16.115	1.00	98.73 N
ATOM	1843	CA	ASN	A	237	19.136	-10.494	15.944	1.00	104.56 C
ATOM	1844	C	ASN	A	237	18.609	-11.196	14.686	1.00	110.81 C
ATOM	1845	O	ASN	A	237	17.530	-11.792	14.705	1.00	112.81 O
ATOM	1846	CB	ASN	A	237	18.759	-9.004	15.930	1.00	100.46 C
ATOM	1847	CG	ASN	A	237	17.268	-8.761	16.142	1.00	100.48 C
ATOM	1848	OD1	ASN	A	237	16.868	-7.689	16.600	1.00	96.36 O
ATOM	1849	ND2	ASN	A	237	16.443	-9.747	15.798	1.00	97.08 N
ATOM	1850	N	GLU	A	238	19.382	-11.111	13.607	1.00	114.86 N
ATOM	1851	CA	GLU	A	238	19.072	-11.709	12.303	1.00	120.04 C
ATOM	1852	C	GLU	A	238	17.688	-12.328	12.095	1.00	121.21 C
ATOM	1853	O	GLU	A	238	16.975	-11.855	11.181	1.00	121.72 O
ATOM	1854	CB	GLU	A	238	20.152	-12.736	11.963	1.00	121.17 C
ATOM	1855	CG	GLU	A	238	21.557	-12.228	12.238	1.00	126.14 C
ATOM	1856	CD	GLU	A	238	21.808	-10.840	11.662	1.00	130.48 C
ATOM	1857	OE1	GLU	A	238	21.090	-9.885	12.034	1.00	132.56 O
ATOM	1858	OE2	GLU	A	238	22.731	-10.705	10.837	1.00	134.55 O
ATOM	1859	N	ASP	A	241	18.070	-14.713	9.305	1.00	127.03 N
ATOM	1860	CA	ASP	A	241	17.685	-16.080	9.767	1.00	127.98 C
ATOM	1861	C	ASP	A	241	17.960	-16.274	11.255	1.00	129.18 C
ATOM	1862	O	ASP	A	241	18.938	-15.754	11.803	1.00	129.01 O
ATOM	1863	CB	ASP	A	241	18.443	-17.152	8.972	1.00	124.42 C
ATOM	1864	CG	ASP	A	241	18.044	-18.574	9.365	1.00	123.20 C
ATOM	1865	OD1	ASP	A	241	18.114	-18.916	10.570	1.00	119.17 O
ATOM	1866	OD2	ASP	A	241	17.664	-19.356	8.464	1.00	120.27 O
ATOM	1867	N	ASP	A	242	17.080	-17.043	11.888	1.00	129.87 N
ATOM	1868	CA	ASP	A	242	17.157	-17.357	13.310	1.00	128.52 C
ATOM	1869	C	ASP	A	242	16.420	-18.676	13.544	1.00	124.12 C
ATOM	1870	O	ASP	A	242	15.291	-18.851	13.081	1.00	127.28 O
ATOM	1871	CB	ASP	A	242	16.509	-16.230	14.128	1.00	134.37 C
ATOM	1872	CG	ASP	A	242	15.076	-15.931	13.693	1.00	137.89 C
ATOM	1873	OD1	ASP	A	242	14.695	-16.306	12.560	1.00	139.91 O
ATOM	1874	OD2	ASP	A	242	14.335	-15.302	14.484	1.00	138.48 O
ATOM	1875	N	GLU	A	243	17.053	-19.614	14.237	1.00	115.47 N
ATOM	1876	CA	GLU	A	243	16.401	-20.892	14.492	1.00	108.81 C
ATOM	1877	C	GLU	A	243	16.219	-21.065	15.984	1.00	101.77 C
ATOM	1878	O	GLU	A	243	15.232	-21.637	16.453	1.00	97.50 O
ATOM	1879	CB	GLU	A	243	17.243	-22.056	13.957	1.00	113.03 C
ATOM	1880	CG	GLU	A	243	18.587	-22.269	14.665	1.00	119.77 C
ATOM	1881	CD	GLU	A	243	19.736	-21.500	14.022	1.00	123.96 C
ATOM	1882	OE1	GLU	A	243	20.004	-21.723	12.821	1.00	128.49 O
ATOM	1883	OE2	GLU	A	243	20.380	-20.682	14.716	1.00	125.21 O
ATOM	1884	N	LYS	A	244	17.193	-20.552	16.719	1.00	90.55 N
ATOM	1885	CA	LYS	A	244	17.196	-20.652	18.159	1.00	87.36 C
ATOM	1886	C	LYS	A	244	16.847	-19.342	18.851	1.00	78.94 C
ATOM	1887	O	LYS	A	244	15.944	-19.299	19.681	1.00	79.48 O
ATOM	1888	CB	LYS	A	244	18.567	-21.157	18.623	1.00	85.94 C
ATOM	1889	CG	LYS	A	244	18.973	-20.687	20.009	1.00	90.77 C
ATOM	1890	CD	LYS	A	244	20.222	-21.392	20.527	1.00	85.35 C
ATOM	1891	CE	LYS	A	244	19.960	-22.872	20.764	1.00	85.15 C
ATOM	1892	NZ	LYS	A	244	18.698	-23.096	21.533	1.00	79.01 N
ATOM	1893	N	HIS	A	245	17.566	-18.279	18.510	1.00	72.67 N
ATOM	1894	CA	HIS	A	245	17.332	-16.978	19.121	1.00	73.65 C
ATOM	1895	C	HIS	A	245	16.275	-16.150	18.398	1.00	71.43 C
ATOM	1896	O	HIS	A	245	16.483	-15.726	17.264	1.00	73.85 O
ATOM	1897	CB	HIS	A	245	18.636	-16.191	19.174	1.00	62.45 C

Table 2

ATOM	1898	CG	HIS	A	245	19.712	-16.860	19.968	1.00	73.56 C
ATOM	1899	ND1	HIS	A	245	19.566	-17.183	21.301	1.00	75.57 N
ATOM	1900	CD2	HIS	A	245	20.963	-17.251	19.624	1.00	74.25 C
ATOM	1901	CE1	HIS	A	245	20.680	-17.740	21.742	1.00	69.91 C
ATOM	1902	NE2	HIS	A	245	21.542	-17.792	20.747	1.00	78.21 N
ATOM	1903	N	ILE	A	246	15.151	-15.907	19.066	1.00	71.28 N
ATOM	1904	CA	ILE	A	246	14.061	-15.117	18.492	1.00	67.47 C
ATOM	1905	C	ILE	A	246	13.820	-13.823	19.279	1.00	68.54 C
ATOM	1906	O	ILE	A	246	13.465	-13.871	20.459	1.00	56.11 O
ATOM	1907	CB	ILE	A	246	12.746	-15.912	18.494	1.00	71.39 C
ATOM	1908	CG1	ILE	A	246	12.953	-17.270	17.829	1.00	73.66 C
ATOM	1909	CG2	ILE	A	246	11.656	-15.114	17.803	1.00	69.42 C
ATOM	1910	CD1	ILE	A	246	13.544	-17.182	16.451	1.00	82.71 C
ATOM	1911	N	PHE	A	247	13.991	-12.675	18.625	1.00	57.64 N
ATOM	1912	CA	PHE	A	247	13.783	-11.395	19.286	1.00	57.66 C
ATOM	1913	C	PHE	A	247	12.444	-10.766	19.000	1.00	59.75 C
ATOM	1914	O	PHE	A	247	11.842	-11.003	17.955	1.00	71.91 O
ATOM	1915	CB	PHE	A	247	14.831	-10.386	18.866	1.00	58.61 C
ATOM	1916	CG	PHE	A	247	16.205	-10.761	19.252	1.00	55.18 C
ATOM	1917	CD1	PHE	A	247	16.931	-11.663	18.486	1.00	63.52 C
ATOM	1918	CD2	PHE	A	247	16.791	-10.195	20.375	1.00	64.94 C
ATOM	1919	CE1	PHE	A	247	18.233	-11.994	18.836	1.00	56.98 C
ATOM	1920	CE2	PHE	A	247	18.084	-10.515	20.735	1.00	62.89 C
ATOM	1921	CZ	PHE	A	247	18.813	-11.416	19.963	1.00	69.14 C
ATOM	1922	N	SER	A	248	11.984	-9.948	19.939	1.00	60.62 N
ATOM	1923	CA	SER	A	248	10.741	-9.211	19.761	1.00	59.42 C
ATOM	1924	C	SER	A	248	11.135	-8.035	18.848	1.00	58.07 C
ATOM	1925	O	SER	A	248	12.324	-7.793	18.605	1.00	50.63 O
ATOM	1926	CB	SER	A	248	10.238	-8.684	21.107	1.00	51.67 C
ATOM	1927	OG	SER	A	248	11.212	-7.849	21.713	1.00	56.47 O
ATOM	1928	N	ASP	A	249	10.156	-7.286	18.364	1.00	62.87 N
ATOM	1929	CA	ASP	A	249	10.433	-6.168	17.461	1.00	68.58 C
ATOM	1930	C	ASP	A	249	11.414	-5.157	18.016	1.00	71.42 C
ATOM	1931	O	ASP	A	249	12.289	-4.649	17.304	1.00	70.32 O
ATOM	1932	CB	ASP	A	249	9.113	-5.519	17.102	1.00	78.97 C
ATOM	1933	CG	ASP	A	249	8.122	-6.538	16.598	1.00	85.41 C
ATOM	1934	OD1	ASP	A	249	8.266	-6.986	15.438	1.00	90.50 O
ATOM	1935	OD2	ASP	A	249	7.218	-6.926	17.370	1.00	85.77 O
ATOM	1936	N	ASP	A	250	11.274	-4.875	19.297	1.00	71.27 N
ATOM	1937	CA	ASP	A	250	12.159	-3.942	19.964	1.00	74.17 C
ATOM	1938	C	ASP	A	250	13.358	-4.713	20.521	1.00	70.10 C
ATOM	1939	O	ASP	A	250	14.337	-4.113	20.971	1.00	70.84 O
ATOM	1940	CB	ASP	A	250	11.390	-3.284	21.100	1.00	82.42 C
ATOM	1941	CG	ASP	A	250	10.583	-4.296	21.895	1.00	86.25 C
ATOM	1942	OD1	ASP	A	250	10.204	-5.350	21.328	1.00	87.71 O
ATOM	1943	OD2	ASP	A	250	10.316	-4.044	23.082	1.00	99.42 O
ATOM	1944	N	SER	A	251	13.266	-6.044	20.478	1.00	61.34 N
ATOM	1945	CA	SER	A	251	14.301	-6.932	21.005	1.00	60.93 C
ATOM	1946	C	SER	A	251	14.357	-6.787	22.529	1.00	55.43 C
ATOM	1947	O	SER	A	251	15.398	-6.997	23.149	1.00	54.55 O
ATOM	1948	CB	SER	A	251	15.667	-6.615	20.386	1.00	56.47 C
ATOM	1949	OG	SER	A	251	15.608	-6.719	18.971	1.00	68.26 O
ATOM	1950	N	SER	A	252	13.222	-6.419	23.120	1.00	44.12 N
ATOM	1951	CA	SER	A	252	13.132	-6.262	24.565	1.00	54.67 C
ATOM	1952	C	SER	A	252	12.961	-7.666	25.142	1.00	45.19 C
ATOM	1953	O	SER	A	252	13.231	-7.900	26.321	1.00	45.23 O
ATOM	1954	CB	SER	A	252	11.948	-5.359	24.957	1.00	50.26 C
ATOM	1955	OG	SER	A	252	10.705	-6.019	24.785	1.00	68.26 O
ATOM	1956	N	GLU	A	253	12.511	-8.586	24.288	1.00	39.14 N

Table 2

ATOM	1957	CA	GLU	A	253	12.351	-9.984	24.655	1.00	42.86 C
ATOM	1958	C	GLU	A	253	13.245	-10.847	23.787	1.00	55.42 C
ATOM	1959	O	GLU	A	253	13.322	-10.649	22.573	1.00	55.46 O
ATOM	1960	CB	GLU	A	253	10.924	-10.475	24.459	1.00	46.35 C
ATOM	1961	CG	GLU	A	253	9.898	-9.823	25.335	1.00	52.21 C
ATOM	1962	CD	GLU	A	253	8.629	-10.640	25.406	1.00	55.68 C
ATOM	1963	OE1	GLU	A	253	8.464	-11.550	24.569	1.00	60.84 O
ATOM	1964	OE2	GLU	A	253	7.792	-10.370	26.296	1.00	63.61 O
ATOM	1965	N	LEU	A	254	13.925	-11.798	24.423	1.00	49.11 N
ATOM	1966	CA	LEU	A	254	14.793	-12.741	23.730	1.00	43.78 C
ATOM	1967	C	LEU	A	254	14.260	-14.129	24.052	1.00	54.16 C
ATOM	1968	O	LEU	A	254	14.179	-14.516	25.221	1.00	49.96 O
ATOM	1969	CB	LEU	A	254	16.240	-12.617	24.212	1.00	48.13 C
ATOM	1970	CG	LEU	A	254	17.132	-13.793	23.786	1.00	61.15 C
ATOM	1971	CD1	LEU	A	254	17.129	-13.902	22.264	1.00	56.30 C
ATOM	1972	CD2	LEU	A	254	18.561	-13.622	24.314	1.00	45.18 C
ATOM	1973	N	THR	A	255	13.874	-14.873	23.024	1.00	52.09 N
ATOM	1974	CA	THR	A	255	13.343	-16.214	23.233	1.00	55.30 C
ATOM	1975	C	THR	A	255	14.371	-17.254	22.822	1.00	57.05 C
ATOM	1976	O	THR	A	255	14.809	-17.279	21.677	1.00	56.25 O
ATOM	1977	CB	THR	A	255	12.050	-16.444	22.419	1.00	62.05 C
ATOM	1978	OG1	THR	A	255	10.999	-15.630	22.951	1.00	66.84 O
ATOM	1979	CG2	THR	A	255	11.625	-17.908	22.491	1.00	69.28 C
ATOM	1980	N	ILE	A	256	14.784	-18.085	23.774	1.00	57.59 N
ATOM	1981	CA	ILE	A	256	15.740	-19.140	23.482	1.00	53.88 C
ATOM	1982	C	ILE	A	256	14.863	-20.362	23.227	1.00	55.73 C
ATOM	1983	O	ILE	A	256	14.031	-20.740	24.050	1.00	53.74 O
ATOM	1984	CB	ILE	A	256	16.721	-19.325	24.635	1.00	60.39 C
ATOM	1985	CG1	ILE	A	256	17.478	-18.003	24.865	1.00	49.75 C
ATOM	1986	CG2	ILE	A	256	17.729	-20.408	24.263	1.00	67.76 C
ATOM	1987	CD1	ILE	A	256	18.337	-17.959	26.113	1.00	52.15 C
ATOM	1988	N	ARG	A	257	15.049	-20.980	22.070	1.00	60.13 N
ATOM	1989	CA	ARG	A	257	14.153	-22.051	21.657	1.00	71.50 C
ATOM	1990	C	ARG	A	257	14.176	-23.516	22.065	1.00	69.32 C
ATOM	1991	O	ARG	A	257	13.160	-24.049	22.523	1.00	80.18 O
ATOM	1992	CB	ARG	A	257	14.007	-21.955	20.148	1.00	74.93 C
ATOM	1993	CG	ARG	A	257	13.281	-20.678	19.720	1.00	86.48 C
ATOM	1994	CD	ARG	A	257	11.972	-21.046	19.067	1.00	94.98 C
ATOM	1995	NE	ARG	A	257	12.243	-22.177	18.190	1.00	102.55 N
ATOM	1996	CZ	ARG	A	257	11.403	-23.175	17.936	1.00	101.10 C
ATOM	1997	NH1	ARG	A	257	10.194	-23.198	18.481	1.00	98.39 N
ATOM	1998	NH2	ARG	A	257	11.805	-24.190	17.182	1.00	99.09 N
ATOM	1999	N	ASN	A	258	15.287	-24.195	21.864	1.00	61.69 N
ATOM	2000	CA	ASN	A	258	15.340	-25.602	22.253	1.00	64.49 C
ATOM	2001	C	ASN	A	258	16.465	-25.618	23.247	1.00	62.07 C
ATOM	2002	O	ASN	A	258	17.624	-25.892	22.925	1.00	55.85 O
ATOM	2003	CB	ASN	A	258	15.636	-26.481	21.041	1.00	66.15 C
ATOM	2004	CG	ASN	A	258	14.404	-26.716	20.191	1.00	68.75 C
ATOM	2005	OD1	ASN	A	258	13.379	-27.234	20.673	1.00	64.25 O
ATOM	2006	ND2	ASN	A	258	14.484	-26.329	18.926	1.00	70.00 N
ATOM	2007	N	VAL	A	259	16.094	-25.272	24.468	1.00	62.90 N
ATOM	2008	CA	VAL	A	259	17.049	-25.157	25.545	1.00	65.80 C
ATOM	2009	C	VAL	A	259	17.876	-26.384	25.872	1.00	58.88 C
ATOM	2010	O	VAL	A	259	17.365	-27.483	26.054	1.00	56.71 O
ATOM	2011	CB	VAL	A	259	16.370	-24.703	26.858	1.00	64.49 C
ATOM	2012	CG1	VAL	A	259	17.433	-24.328	27.883	1.00	63.04 C
ATOM	2013	CG2	VAL	A	259	15.437	-23.546	26.599	1.00	62.50 C
ATOM	2014	N	ASP	A	260	19.176	-26.159	25.951	1.00	60.37 N
ATOM	2015	CA	ASP	A	260	20.110	-27.191	26.329	1.00	64.76 C

Table 2

ATOM	2016	C	ASP	A	260	21.141	-26.491	27.190	1.00	63.70 C
ATOM	2017	O	ASP	A	260	21.185	-25.257	27.253	1.00	55.60 O
ATOM	2018	CB	ASP	A	260	20.785	-27.829	25.120	1.00	61.25 C
ATOM	2019	CG	ASP	A	260	21.602	-26.844	24.322	1.00	68.49 C
ATOM	2020	OD1	ASP	A	260	22.091	-25.847	24.896	1.00	68.44 O
ATOM	2021	OD2	ASP	A	260	21.775	-27.084	23.110	1.00	81.31 O
ATOM	2022	N	LYS	A	261	21.986	-27.277	27.832	1.00	57.12 N
ATOM	2023	CA	LYS	A	261	22.985	-26.711	28.711	1.00	51.64 C
ATOM	2024	C	LYS	A	261	23.832	-25.591	28.141	1.00	46.97 C
ATOM	2025	O	LYS	A	261	24.335	-24.757	28.895	1.00	48.66 O
ATOM	2026	CB	LYS	A	261	23.874	-27.828	29.258	1.00	52.71 C
ATOM	2027	CG	LYS	A	261	23.193	-28.612	30.358	1.00	61.87 C
ATOM	2028	CD	LYS	A	261	24.105	-29.669	30.947	1.00	73.37 C
ATOM	2029	CE	LYS	A	261	23.600	-30.117	32.308	1.00	76.85 C
ATOM	2030	NZ	LYS	A	261	23.680	-29.007	33.304	1.00	77.99 N
ATOM	2031	N	ASN	A	262	24.004	-25.534	26.827	1.00	51.62 N
ATOM	2032	CA	ASN	A	262	24.834	-24.464	26.278	1.00	50.71 C
ATOM	2033	C	ASN	A	262	24.189	-23.099	26.414	1.00	49.52 C
ATOM	2034	O	ASN	A	262	24.835	-22.073	26.224	1.00	44.29 O
ATOM	2035	CB	ASN	A	262	25.160	-24.707	24.815	1.00	63.69 C
ATOM	2036	CG	ASN	A	262	26.545	-25.256	24.636	1.00	76.99 C
ATOM	2037	OD1	ASN	A	262	27.466	-24.881	25.368	1.00	88.03 O
ATOM	2038	ND2	ASN	A	262	26.713	-26.145	23.664	1.00	83.71 N
ATOM	2039	N	ASP	A	263	22.911	-23.100	26.755	1.00	43.87 N
ATOM	2040	CA	ASP	A	263	22.173	-21.864	26.915	1.00	49.29 C
ATOM	2041	C	ASP	A	263	22.341	-21.257	28.307	1.00	56.55 C
ATOM	2042	O	ASP	A	263	21.984	-20.103	28.532	1.00	45.77 O
ATOM	2043	CB	ASP	A	263	20.705	-22.115	26.593	1.00	46.15 C
ATOM	2044	CG	ASP	A	263	20.502	-22.558	25.148	1.00	47.16 C
ATOM	2045	OD1	ASP	A	263	21.208	-22.006	24.272	1.00	50.06 O
ATOM	2046	OD2	ASP	A	263	19.642	-23.440	24.894	1.00	53.96 O
ATOM	2047	N	GLU	A	264	22.886	-22.033	29.241	1.00	52.20 N
ATOM	2048	CA	GLU	A	264	23.126	-21.517	30.580	1.00	50.47 C
ATOM	2049	C	GLU	A	264	24.217	-20.455	30.464	1.00	55.25 C
ATOM	2050	O	GLU	A	264	25.286	-20.722	29.917	1.00	51.52 O
ATOM	2051	CB	GLU	A	264	23.575	-22.644	31.526	1.00	49.18 C
ATOM	2052	CG	GLU	A	264	23.865	-22.150	32.948	1.00	56.13 C
ATOM	2053	CD	GLU	A	264	24.070	-23.270	33.968	1.00	59.96 C
ATOM	2054	OE1	GLU	A	264	23.144	-24.088	34.166	1.00	52.27 O
ATOM	2055	OE2	GLU	A	264	25.161	-23.319	34.575	1.00	63.96 O
ATOM	2056	N	ALA	A	265	23.936	-19.254	30.971	1.00	50.58 N
ATOM	2057	CA	ALA	A	265	24.882	-18.143	30.932	1.00	49.56 C
ATOM	2058	C	ALA	A	265	24.285	-16.892	31.553	1.00	44.28 C
ATOM	2059	O	ALA	A	265	23.138	-16.876	32.020	1.00	44.60 O
ATOM	2060	CB	ALA	A	265	25.275	-17.839	29.485	1.00	55.17 C
ATOM	2061	N	GLU	A	266	25.084	-15.837	31.565	1.00	46.95 N
ATOM	2062	CA	GLU	A	266	24.597	-14.566	32.052	1.00	58.95 C
ATOM	2063	C	GLU	A	266	24.233	-13.782	30.796	1.00	54.06 C
ATOM	2064	O	GLU	A	266	25.077	-13.547	29.937	1.00	49.16 O
ATOM	2065	CB	GLU	A	266	25.662	-13.784	32.824	1.00	49.59 C
ATOM	2066	CG	GLU	A	266	25.188	-12.371	33.185	1.00	68.76 C
ATOM	2067	CD	GLU	A	266	26.312	-11.461	33.655	1.00	79.04 C
ATOM	2068	OE1	GLU	A	266	27.442	-11.585	33.135	1.00	92.30 O
ATOM	2069	OE2	GLU	A	266	26.071	-10.604	34.534	1.00	84.00 O
ATOM	2070	N	TYR	A	267	22.969	-13.405	30.682	1.00	56.50 N
ATOM	2071	CA	TYR	A	267	22.539	-12.620	29.539	1.00	53.55 C
ATOM	2072	C	TYR	A	267	22.379	-11.175	29.973	1.00	53.33 C
ATOM	2073	O	TYR	A	267	21.857	-10.899	31.051	1.00	56.26 O
ATOM	2074	CB	TYR	A	267	21.216	-13.131	29.000	1.00	41.05 C

ATOM	2075	CG	TYR	A	267	21.302	-14.503	28.392	1.00	52.19 C
ATOM	2076	CD1	TYR	A	267	21.310	-15.645	29.200	1.00	46.18 C
ATOM	2077	CD2	TYR	A	267	21.374	-14.669	27.010	1.00	42.85 C
ATOM	2078	CE1	TYR	A	267	21.385	-16.907	28.649	1.00	36.41 C
ATOM	2079	CE2	TYR	A	267	21.447	-15.926	26.447	1.00	47.87 C
ATOM	2080	CZ	TYR	A	267	21.454	-17.043	27.269	1.00	46.20 C
ATOM	2081	OH	TYR	A	267	21.534	-18.289	26.709	1.00	46.42 O
ATOM	2082	N	VAL	A	268	22.849	-10.259	29.134	1.00	54.55 N
ATOM	2083	CA	VAL	A	268	22.744	-8.833	29.420	1.00	51.27 C
ATOM	2084	C	VAL	A	268	21.939	-8.121	28.325	1.00	53.04 C
ATOM	2085	O	VAL	A	268	22.238	-8.268	27.140	1.00	49.32 O
ATOM	2086	CB	VAL	A	268	24.149	-8.164	29.507	1.00	51.72 C
ATOM	2087	CG1	VAL	A	268	24.008	-6.653	29.697	1.00	53.25 C
ATOM	2088	CG2	VAL	A	268	24.954	-8.757	30.667	1.00	53.72 C
ATOM	2089	N	CYS	A	269	20.909	-7.372	28.708	1.00	47.02 N
ATOM	2090	CA	CYS	A	269	20.130	-6.631	27.712	1.00	46.07 C
ATOM	2091	C	CYS	A	269	20.572	-5.192	27.825	1.00	48.28 C
ATOM	2092	O	CYS	A	269	20.513	-4.568	28.893	1.00	54.75 O
ATOM	2093	CB	CYS	A	269	18.645	-6.725	27.972	1.00	47.89 C
ATOM	2094	SG	CYS	A	269	18.154	-5.060	29.588	1.00	57.20 S
ATOM	2095	N	ILE	A	270	21.040	-4.684	26.705	1.00	44.49 N
ATOM	2096	CA	ILE	A	270	21.542	-3.334	26.618	1.00	54.21 C
ATOM	2097	C	ILE	A	270	20.492	-2.429	25.984	1.00	51.98 C
ATOM	2098	O	ILE	A	270	20.057	-2.665	24.858	1.00	52.39 O
ATOM	2099	CB	ILE	A	270	22.804	-3.333	25.757	1.00	58.16 C
ATOM	2100	CG1	ILE	A	270	23.777	-4.385	26.287	1.00	59.14 C
ATOM	2101	CG2	ILE	A	270	23.451	-1.964	25.768	1.00	58.07 C
ATOM	2102	CD1	ILE	A	270	24.907	-4.698	25.332	1.00	62.65 C
ATOM	2103	N	ALA	A	271	20.068	-1.413	26.725	1.00	46.08 N
ATOM	2104	CA	ALA	A	271	19.081	-0.463	26.220	1.00	43.82 C
ATOM	2105	C	ALA	A	271	19.811	0.838	25.863	1.00	41.91 C
ATOM	2106	O	ALA	A	271	20.461	1.454	26.713	1.00	41.51 O
ATOM	2107	CB	ALA	A	271	18.010	-0.212	27.272	1.00	40.50 C
ATOM	2108	N	GLU	A	272	19.709	1.242	24.601	1.00	43.98 N
ATOM	2109	CA	GLU	A	272	20.375	2.453	24.128	1.00	50.40 C
ATOM	2110	C	GLU	A	272	19.526	3.346	23.255	1.00	40.39 C
ATOM	2111	O	GLU	A	272	18.635	2.880	22.548	1.00	43.66 O
ATOM	2112	CB	GLU	A	272	21.589	2.115	23.251	1.00	46.89 C
ATOM	2113	CG	GLU	A	272	22.738	1.366	23.863	1.00	76.32 C
ATOM	2114	CD	GLU	A	272	23.835	1.101	22.832	1.00	88.35 C
ATOM	2115	OE1	GLU	A	272	23.496	0.886	21.643	1.00	95.66 O
ATOM	2116	OE2	GLU	A	272	25.031	1.096	23.206	1.00	91.47 O
ATOM	2117	N	ASN	A	273	19.843	4.635	23.316	1.00	46.76 N
ATOM	2118	CA	ASN	A	273	19.260	5.648	22.438	1.00	47.59 C
ATOM	2119	C	ASN	A	273	20.335	6.718	22.340	1.00	52.11 C
ATOM	2120	O	ASN	A	273	21.366	6.622	23.008	1.00	44.76 O
ATOM	2121	CB	ASN	A	273	17.897	6.201	22.916	1.00	46.27 C
ATOM	2122	CG	ASN	A	273	17.964	6.980	24.211	1.00	44.51 C
ATOM	2123	OD1	ASN	A	273	19.012	7.471	24.611	1.00	44.37 O
ATOM	2124	ND2	ASN	A	273	16.808	7.126	24.866	1.00	38.00 N
ATOM	2125	N	LYS	A	274	20.128	7.723	21.504	1.00	56.80 N
ATOM	2126	CA	LYS	A	274	21.154	8.740	21.317	1.00	51.83 C
ATOM	2127	C	LYS	A	274	21.618	9.485	22.567	1.00	54.11 C
ATOM	2128	O	LYS	A	274	22.667	10.123	22.545	1.00	58.51 O
ATOM	2129	CB	LYS	A	274	20.718	9.742	20.238	1.00	55.02 C
ATOM	2130	CG	LYS	A	274	19.590	10.658	20.644	1.00	47.96 C
ATOM	2131	CD	LYS	A	274	18.892	11.218	19.403	1.00	52.54 C
ATOM	2132	CE	LYS	A	274	19.784	12.175	18.622	1.00	65.50 C
ATOM	2133	NZ	LYS	A	274	19.120	12.652	17.364	1.00	68.41 N

Table 2

ATOM	2134	N	ALA	A	275	20.869	9.403	23.659	1.00	47.65 N
ATOM	2135	CA	ALA	A	275	21.275	10.100	24.868	1.00	48.41 C
ATOM	2136	C	ALA	A	275	21.944	9.233	25.930	1.00	49.48 C
ATOM	2137	O	ALA	A	275	22.294	9.735	26.988	1.00	50.34 O
ATOM	2138	CB	ALA	A	275	20.084	10.814	25.487	1.00	44.55 C
ATOM	2139	N	GLY	A	276	22.122	7.942	25.691	1.00	49.34 N
ATOM	2140	CA	GLY	A	276	22.755	7.177	26.746	1.00	51.88 C
ATOM	2141	C	GLY	A	276	22.482	5.694	26.738	1.00	50.21 C
ATOM	2142	O	GLY	A	276	21.907	5.164	25.779	1.00	51.48 O
ATOM	2143	N	GLU	A	277	22.868	5.026	27.824	1.00	50.99 N
ATOM	2144	CA	GLU	A	277	22.696	3.586	27.906	1.00	53.05 C
ATOM	2145	C	GLU	A	277	22.598	3.056	29.316	1.00	51.11 C
ATOM	2146	O	GLU	A	277	23.116	3.655	30.249	1.00	52.33 O
ATOM	2147	CB	GLU	A	277	23.873	2.915	27.194	1.00	58.98 C
ATOM	2148	CG	GLU	A	277	23.900	1.389	27.218	1.00	74.31 C
ATOM	2149	CD	GLU	A	277	24.570	0.797	28.462	1.00	89.46 C
ATOM	2150	OE1	GLU	A	277	25.277	1.537	29.183	1.00	96.28 O
ATOM	2151	OE2	GLU	A	277	24.398	-0.420	28.705	1.00	89.19 O
ATOM	2152	N	GLN	A	278	21.907	1.927	29.453	1.00	49.66 N
ATOM	2153	CA	GLN	A	278	21.783	1.228	30.724	1.00	45.13 C
ATOM	2154	C	GLN	A	278	21.513	-0.239	30.415	1.00	50.42 C
ATOM	2155	O	GLN	A	278	20.877	-0.568	29.417	1.00	46.75 O
ATOM	2156	CB	GLN	A	278	20.662	1.789	31.607	1.00	48.09 C
ATOM	2157	CG	GLN	A	278	20.812	1.327	33.064	1.00	46.69 C
ATOM	2158	CD	GLN	A	278	19.700	1.822	33.976	1.00	57.97 C
ATOM	2159	OE1	GLN	A	278	18.572	1.330	33.917	1.00	44.46 O
ATOM	2160	NE2	GLN	A	278	20.012	2.800	34.826	1.00	53.33 N
ATOM	2161	N	ASP	A	279	22.013	-1.132	31.257	1.00	45.92 N
ATOM	2162	CA	ASP	A	279	21.795	-2.541	31.014	1.00	47.69 C
ATOM	2163	C	ASP	A	279	21.345	-3.251	32.270	1.00	47.71 C
ATOM	2164	O	ASP	A	279	21.357	-2.687	33.366	1.00	48.35 O
ATOM	2165	CB	ASP	A	279	23.062	-3.186	30.451	1.00	60.02 C
ATOM	2166	CG	ASP	A	279	24.316	-2.707	31.154	1.00	69.17 C
ATOM	2167	OD1	ASP	A	279	24.456	-2.954	32.370	1.00	75.17 O
ATOM	2168	OD2	ASP	A	279	25.157	-2.073	30.490	1.00	75.70 O
ATOM	2169	N	ALA	A	280	20.892	-4.480	32.079	1.00	49.27 N
ATOM	2170	CA	ALA	A	280	20.428	-5.314	33.172	1.00	57.28 C
ATOM	2171	C	ALA	A	280	20.804	-6.748	32.833	1.00	54.10 C
ATOM	2172	O	ALA	A	280	20.868	-7.126	31.659	1.00	47.63 O
ATOM	2173	CB	ALA	A	280	18.909	-5.184	33.341	1.00	47.77 C
ATOM	2174	N	SER	A	281	21.043	-7.560	33.854	1.00	53.68 N
ATOM	2175	CA	SER	A	281	21.429	-8.931	33.599	1.00	48.69 C
ATOM	2176	C	SER	A	281	20.402	-9.952	34.031	1.00	45.20 C
ATOM	2177	O	SER	A	281	19.595	-9.718	34.934	1.00	45.89 O
ATOM	2178	CB	SER	A	281	22.768	-9.219	34.279	1.00	61.38 C
ATOM	2179	OG	SER	A	281	22.718	-8.863	35.646	1.00	57.59 O
ATOM	2180	N	ILE	A	282	20.427	-11.086	33.349	1.00	43.38 N
ATOM	2181	CA	ILE	A	282	19.524	-12.185	33.637	1.00	41.38 C
ATOM	2182	C	ILE	A	282	20.392	-13.429	33.671	1.00	47.86 C
ATOM	2183	O	ILE	A	282	21.235	-13.631	32.799	1.00	51.03 O
ATOM	2184	CB	ILE	A	282	18.436	-12.316	32.548	1.00	40.14 C
ATOM	2185	CG1	ILE	A	282	17.557	-11.056	32.557	1.00	46.94 C
ATOM	2186	CG2	ILE	A	282	17.576	-13.549	32.807	1.00	42.53 C
ATOM	2187	CD1	ILE	A	282	16.484	-10.998	31.476	1.00	45.40 C
ATOM	2188	N	HIS	A	283	20.204	-14.248	34.695	1.00	45.39 N
ATOM	2189	CA	HIS	A	283	20.998	-15.458	34.816	1.00	46.01 C
ATOM	2190	C	HIS	A	283	20.145	-16.651	34.501	1.00	41.84 C
ATOM	2191	O	HIS	A	283	19.164	-16.923	35.197	1.00	51.27 O
ATOM	2192	CB	HIS	A	283	21.570	-15.575	36.230	1.00	53.96 C

Table 2

ATOM	2193	CG	HIS	A	283	22.617	-14.551	36.543	1.00	60.28 C
ATOM	2194	ND1	HIS	A	283	23.908	-14.633	36.065	1.00	69.25 N
ATOM	2195	CD2	HIS	A	283	22.554	-13.401	37.260	1.00	68.71 C
ATOM	2196	CE1	HIS	A	283	24.593	-13.578	36.473	1.00	75.43 C
ATOM	2197	NE2	HIS	A	283	23.796	-12.816	37.199	1.00	66.88 N
ATOM	2198	N	LEU	A	284	20.499	-17.349	33.427	1.00	41.70 N
ATOM	2199	CA	LEU	A	284	19.752	-18.534	33.050	1.00	45.86 C
ATOM	2200	C	LEU	A	284	20.533	-19.778	33.469	1.00	49.53 C
ATOM	2201	O	LEU	A	284	21.683	-19.963	33.058	1.00	45.44 O
ATOM	2202	CB	LEU	A	284	19.515	-18.576	31.532	1.00	41.74 C
ATOM	2203	CG	LEU	A	284	18.782	-19.827	31.028	1.00	47.91 C
ATOM	2204	CD1	LEU	A	284	17.407	-19.888	31.680	1.00	45.59 C
ATOM	2205	CD2	LEU	A	284	18.648	-19.810	29.500	1.00	48.70 C
ATOM	2206	N	LYS	A	285	19.913	-20.625	34.285	1.00	48.59 N
ATOM	2207	CA	LYS	A	285	20.557	-21.863	34.711	1.00	53.60 C
ATOM	2208	C	LYS	A	285	19.797	-23.008	34.061	1.00	46.75 C
ATOM	2209	O	LYS	A	285	18.570	-23.061	34.109	1.00	49.33 O
ATOM	2210	CB	LYS	A	285	20.531	-21.991	36.239	1.00	56.58 C
ATOM	2211	CG	LYS	A	285	21.302	-20.880	36.942	1.00	63.01 C
ATOM	2212	CD	LYS	A	285	21.254	-21.021	38.459	1.00	71.05 C
ATOM	2213	CE	LYS	A	285	21.853	-19.795	39.148	1.00	76.77 C
ATOM	2214	NZ	LYS	A	285	20.993	-18.583	39.020	1.00	73.22 N
ATOM	2215	N	VAL	A	286	20.525	-23.922	33.436	1.00	44.47 N
ATOM	2216	CA	VAL	A	286	19.888	-25.047	32.759	1.00	53.73 C
ATOM	2217	C	VAL	A	286	20.271	-26.367	33.410	1.00	58.55 C
ATOM	2218	O	VAL	A	286	21.446	-26.709	33.489	1.00	58.02 O
ATOM	2219	CB	VAL	A	286	20.283	-25.078	31.268	1.00	49.11 C
ATOM	2220	CG1	VAL	A	286	19.618	-26.248	30.572	1.00	52.83 C
ATOM	2221	CG2	VAL	A	286	19.872	-23.760	30.597	1.00	49.45 C
ATOM	2222	N	PHE	A	287	19.267	-27.100	33.875	1.00	56.62 N
ATOM	2223	CA	PHE	A	287	19.493	-28.379	34.528	1.00	60.81 C
ATOM	2224	C	PHE	A	287	19.172	-29.540	33.607	1.00	64.78 C
ATOM	2225	O	PHE	A	287	18.208	-29.487	32.846	1.00	64.16 O
ATOM	2226	CB	PHE	A	287	18.645	-28.461	35.795	1.00	58.95 C
ATOM	2227	CG	PHE	A	287	18.868	-27.314	36.724	1.00	61.24 C
ATOM	2228	CD1	PHE	A	287	17.963	-26.259	36.783	1.00	56.19 C
ATOM	2229	CD2	PHE	A	287	20.036	-27.237	37.477	1.00	62.69 C
ATOM	2230	CE1	PHE	A	287	18.224	-25.139	37.575	1.00	53.03 C
ATOM	2231	CE2	PHE	A	287	20.304	-26.124	38.266	1.00	58.31 C
ATOM	2232	CZ	PHE	A	287	19.397	-25.073	38.314	1.00	59.07 C
ATOM	2233	N	ALA	A	288	19.997	-30.583	33.666	1.00	66.33 N
ATOM	2234	CA	ALA	A	288	19.795	-31.766	32.834	1.00	73.18 C
ATOM	2235	C	ALA	A	288	18.428	-32.377	33.119	1.00	78.08 C
ATOM	2236	O	ALA	A	288	17.960	-32.349	34.259	1.00	78.39 O
ATOM	2237	CB	ALA	A	288	20.887	-32.785	33.106	1.00	69.96 C
ATOM	2238	N	LYS	A	289	17.794	-32.931	32.087	1.00	80.55 N
ATOM	2239	CA	LYS	A	289	16.476	-33.541	32.240	1.00	84.08 C
ATOM	2240	C	LYS	A	289	16.535	-34.855	33.016	1.00	88.56 C
ATOM	2241	O	LYS	A	289	15.585	-35.127	33.785	1.00	92.60 O
ATOM	2242	CB	LYS	A	289	15.830	-33.779	30.872	1.00	82.11 C
ATOM	2243	CG	LYS	A	289	16.538	-34.804	30.009	1.00	82.83 C
ATOM	2244	CD	LYS	A	289	15.739	-35.066	28.748	1.00	81.13 C
ATOM	2245	CE	LYS	A	289	16.362	-36.164	27.910	1.00	87.98 C
ATOM	2246	NZ	LYS	A	289	15.562	-36.424	26.677	1.00	90.82 N
ATOM	2247	OXT	LYS	A	289	17.519	-35.608	32.835	1.00	94.14 O
TER	2248		LYS	A	289					
HETATM	2249	O	HOH		1	26.862	53.829	-2.499	1.00	53.80 O
HETATM	2250	O	HOH		2	31.435	56.206	-5.661	1.00	53.53 O
HETATM	2251	O	HOH		4	18.815	60.633	-12.908	1.00	43.98 O

HETATM	2252	O	HOH	5	16.291	34.157	5.585	1.00	64.41 O
HETATM	2253	O	HOH	6	24.283	23.825	11.233	1.00	59.48 O
HETATM	2254	O	HOH	7	21.204	19.365	17.749	1.00	60.83 O
HETATM	2255	O	HOH	8	15.430	12.803	19.226	1.00	45.67 O
HETATM	2256	O	HOH	9	22.245	15.815	31.410	1.00	50.19 O
HETATM	2257	O	HOH	10	25.429	21.325	30.709	1.00	49.37 O
HETATM	2258	O	HOH	11	23.048	36.010	15.248	1.00	51.13 O
HETATM	2259	O	HOH	12	29.692	33.165	19.866	1.00	37.03 O
HETATM	2260	O	HOH	13	9.169	23.139	31.247	1.00	61.40 O
HETATM	2261	O	HOH	14	17.022	56.166	8.038	1.00	75.27 O
HETATM	2262	O	HOH	15	8.769	40.002	7.174	1.00	48.91 O
HETATM	2263	O	HOH	16	10.231	43.238	7.473	1.00	47.42 O
HETATM	2264	O	HOH	17	15.641	26.081	5.720	1.00	78.13 O
HETATM	2265	O	HOH	18	20.551	14.627	22.658	1.00	46.05 O
HETATM	2266	O	HOH	19	11.221	-2.472	26.804	1.00	52.85 O
HETATM	2267	O	HOH	20	13.041	60.224	-4.320	1.00	64.49 O
HETATM	2268	O	HOH	21	14.835	48.897	-2.048	1.00	85.96 O
HETATM	2269	O	HOH	22	29.546	51.498	-21.147	1.00	47.61 O
HETATM	2270	O	HOH	23	24.511	42.141	-28.698	1.00	76.55 O
HETATM	2271	O	HOH	25	21.636	45.365	-18.499	1.00	37.40 O
HETATM	2272	O	HOH	26	15.790	47.805	-19.728	1.00	64.11 O
HETATM	2273	O	HOH	27	20.999	58.533	-6.980	1.00	47.49 O
HETATM	2274	O	HOH	28	14.534	40.436	5.659	1.00	59.32 O
HETATM	2275	O	HOH	29	18.746	16.322	14.473	1.00	79.28 O
HETATM	2276	O	HOH	30	25.965	40.212	9.533	1.00	52.16 O
HETATM	2277	O	HOH	31	16.482	55.396	13.144	1.00	59.76 O
HETATM	2278	O	HOH	32	9.922	15.732	20.883	1.00	48.37 O
HETATM	2279	O	HOH	33	11.915	-0.137	41.445	1.00	73.91 O
HETATM	2280	O	HOH	34	11.044	7.531	19.815	1.00	49.89 O
HETATM	2281	O	HOH	35	6.902	3.742	25.922	1.00	63.36 O
HETATM	2282	O	HOH	37	21.399	-1.338	20.994	1.00	76.17 O
HETATM	2283	O	HOH	38	18.329	53.773	-1.977	1.00	62.61 O
HETATM	2284	O	HOH	39	18.014	43.718	-2.937	1.00	49.73 O
HETATM	2285	O	HOH	40	32.281	40.568	-12.177	1.00	66.60 O
HETATM	2286	O	HOH	41	19.381	44.469	-19.805	1.00	64.16 O
HETATM	2287	O	HOH	42	25.046	41.566	-20.577	1.00	61.50 O
HETATM	2288	O	HOH	46	7.104	2.690	28.661	1.00	90.82 O
HETATM	2289	O	HOH	48	29.774	-14.171	32.170	1.00	72.60 O
HETATM	2290	O	HOH	49	36.677	48.530	-18.261	1.00	57.32 O
HETATM	2291	O	HOH	50	33.317	46.204	-17.946	1.00	47.09 O
HETATM	2292	O	HOH	52	22.357	37.802	16.682	1.00	62.95 O
HETATM	2293	O	HOH	54	11.598	9.583	18.307	1.00	51.71 O
HETATM	2294	O	HOH	55	22.448	12.959	33.086	1.00	71.24 O
HETATM	2295	O	HOH	56	12.323	-25.457	30.778	1.00	69.54 O
HETATM	2296	O	HOH	57	22.080	16.779	21.536	1.00	49.07 O
HETATM	2297	O	HOH	58	17.068	4.212	19.556	1.00	71.54 O
HETATM	2298	O	HOH	59	21.824	23.695	19.290	1.00	44.38 O
HETATM	2299	O	HOH	60	17.965	7.263	19.831	1.00	45.41 O
HETATM	2300	O	HOH	61	19.593	-1.710	35.113	1.00	49.69 O
HETATM	2301	O	HOH	62	18.642	-7.793	36.955	1.00	68.54 O
HETATM	2302	O	HOH	63	23.848	-0.227	33.498	1.00	54.90 O
HETATM	2303	O	HOH	64	31.052	-17.541	34.986	1.00	68.80 O
HETATM	2304	O	HOH	65	5.551	-4.238	9.968	1.00	64.86 O
HETATM	2305	O	HOH	66	10.472	-3.423	9.588	1.00	81.77 O
HETATM	2306	O	HOH	67	6.705	-3.198	12.269	1.00	59.36 O
HETATM	2307	O	HOH	68	18.934	8.523	16.255	1.00	70.67 O
HETATM	2308	O	HOH	69	26.373	-11.223	28.910	1.00	53.04 O
HETATM	2309	O	HOH	70	26.631	6.184	27.729	1.00	74.30 O
HETATM	2310	O	HOH	71	26.466	-20.918	34.876	1.00	70.68 O

HETATM	2311	O	HOH	72	8.293	12.647	18.395	1.00	56.61 O
HETATM	2312	O	HOH	74	17.106	-5.693	36.496	1.00	48.96 O
HETATM	2313	O	HOH	75	1.311	-8.583	8.383	1.00	70.05 O
HETATM	2314	O	HOH	76	26.233	40.015	4.081	1.00	64.69 O
HETATM	2315	O	HOH	77	21.018	39.423	0.780	1.00	63.73 O
HETATM	2316	O	HOH	78	30.385	47.077	-9.984	1.00	47.01 O
HETATM	2317	O	HOH	80	17.757	22.465	9.580	1.00	54.37 O
HETATM	2318	O	HOH	81	25.847	39.446	18.635	1.00	61.83 O
HETATM	2319	O	HOH	82	23.903	-18.248	35.163	1.00	66.46 O
HETATM	2320	O	HOH	83	17.550	29.059	7.625	1.00	69.50 O
HETATM	2321	O	HOH	84	22.192	30.581	38.779	1.00	45.18 O
HETATM	2322	O	HOH	85	19.724	26.758	8.865	1.00	62.11 O
HETATM	2323	O	HOH	87	29.601	58.691	-24.045	1.00	49.94 O
HETATM	2324	O	HOH	88	22.701	60.581	-7.832	1.00	65.08 O
HETATM	2325	O	HOH	89	21.940	62.739	-12.104	1.00	60.23 O
HETATM	2326	O	HOH	90	28.142	44.638	-19.542	1.00	52.86 O
HETATM	2327	O	HOH	91	19.926	59.567	-10.713	1.00	54.05 O
HETATM	2328	O	HOH	92	23.841	23.097	24.364	1.00	55.20 O
HETATM	2329	O	HOH	93	14.026	37.104	24.024	1.00	50.35 O
HETATM	2330	O	HOH	94	28.637	30.316	16.747	1.00	47.63 O
HETATM	2331	O	HOH	95	13.597	-12.079	32.292	1.00	47.38 O
HETATM	2332	O	HOH	96	20.525	6.030	31.726	1.00	59.12 O
HETATM	2333	O	HOH	97	12.219	25.294	38.142	1.00	74.46 O
HETATM	2334	O	HOH	98	17.582	46.166	-21.327	1.00	58.26 O
HETATM	2335	O	HOH	99	18.462	3.098	17.614	1.00	74.29 O
HETATM	2336	O	HOH	100	7.657	-6.217	21.068	1.00	54.31 O
HETATM	2337	O	HOH	101	31.973	58.468	-22.566	1.00	51.37 O
HETATM	2338	O	HOH	102	25.581	34.891	15.303	1.00	62.92 O
HETATM	2339	O	HOH	103	9.781	4.793	26.865	1.00	52.97 O
HETATM	2340	O	HOH	104	27.113	28.768	14.346	1.00	46.27 O
HETATM	2341	O	HOH	105	20.934	59.591	-4.091	1.00	63.10 O
HETATM	2342	O	HOH	106	29.101	39.039	-6.576	1.00	50.94 O
HETATM	2343	O	HOH	107	20.829	-6.266	36.888	1.00	67.77 O
HETATM	2344	O	HOH	108	14.801	-6.395	38.213	1.00	57.81 O
HETATM	2345	O	HOH	109	21.412	-19.178	24.173	1.00	57.65 O
HETATM	2346	O	HOH	110	29.742	32.206	15.564	1.00	51.50 O
HETATM	2347	O	HOH	111	27.197	38.482	-3.772	1.00	57.43 O
HETATM	2348	O	HOH	112	23.730	20.567	24.733	1.00	63.78 O
HETATM	2349	O	HOH	113	15.996	50.339	-4.519	1.00	68.59 O
HETATM	2350	O	HOH	114	10.665	-4.867	34.503	1.00	53.34 O
HETATM	2351	O	HOH	115	6.955	17.535	26.540	1.00	72.17 O
HETATM	2352	O	HOH	116	15.712	-29.078	24.014	1.00	65.77 O
HETATM	2353	O	HOH	118	32.255	44.366	-7.537	1.00	62.15 O
HETATM	2354	O	HOH	119	29.827	41.068	-0.664	1.00	57.67 O
HETATM	2355	O	HOH	122	14.630	-27.859	26.706	1.00	65.41 O
HETATM	2356	O	HOH	123	8.521	-18.764	25.803	1.00	74.48 O
HETATM	2357	O	HOH	125	15.199	60.049	-13.759	1.00	63.41 O
HETATM	2358	O	HOH	126	10.378	14.473	18.707	1.00	52.05 O
HETATM	2359	O	HOH	127	28.187	-10.553	30.862	1.00	65.81 O
HETATM	2360	O	HOH	128	7.837	37.705	8.662	1.00	62.54 O
HETATM	2361	O	HOH	130	23.744	37.155	1.565	1.00	65.13 O
HETATM	2362	O	HOH	131	13.354	57.052	-9.380	1.00	64.16 O
HETATM	2363	O	HOH	132	31.235	44.417	-16.467	1.00	58.09 O
HETATM	2364	O	HOH	134	18.966	44.757	7.268	1.00	51.54 O
HETATM	2365	O	HOH	135	22.888	3.287	35.759	1.00	66.29 O
HETATM	2366	O	HOH	136	10.345	29.244	10.371	1.00	53.80 O
HETATM	2367	O	HOH	137	21.314	-8.331	20.298	1.00	59.91 O
HETATM	2368	O	HOH	138	38.747	55.169	-17.210	1.00	61.68 O
HETATM	2369	O	HOH	139	14.760	55.271	10.174	1.00	55.52 O

Table 2

HETATM	2370	O	HOH	140	23.711	55.591	3.512	1.00	78.73 O
HETATM	2371	O	HOH	142	5.285	37.922	7.977	1.00	63.10 O
HETATM	2372	O	HOH	143	24.355	15.578	30.186	1.00	68.63 O
HETATM	2373	O	HOH	144	23.201	9.987	31.463	1.00	64.84 O
HETATM	2374	O	HOH	145	15.111	-8.434	40.304	1.00	70.85 O
HETATM	2375	O	HOH	146	34.105	49.705	-9.362	1.00	66.43 O
HETATM	2376	O	HOH	147	22.545	50.730	2.853	1.00	70.28 O
HETATM	2377	O	HOH	149	23.888	38.804	-17.868	1.00	69.84 O
HETATM	2378	O	HOH	150	26.301	66.907	-32.270	1.00	69.82 O
HETATM	2379	O	HOH	151	29.578	51.924	-24.078	1.00	67.26 O
HETATM	2380	O	HOH	152	31.935	49.759	-6.982	1.00	72.11 O
HETATM	2381	O	HOH	153	11.771	12.964	31.927	1.00	70.57 O
HETATM	2382	O	HOH	154	14.696	6.619	31.148	1.00	64.86 O
HETATM	2383	O	HOH	155	33.398	69.714	-31.980	1.00	74.81 O
HETATM	2384	O	HOH	156	26.480	50.982	0.230	1.00	59.10 O
HETATM	2385	O	HOH	157	22.798	7.195	30.848	1.00	68.26 O
HETATM	2386	O	HOH	158	19.477	-6.906	18.703	1.00	72.82 O
HETATM	2387	O	HOH	159	13.208	60.522	-15.082	1.00	57.68 O
HETATM	2388	O	HOH	160	34.799	47.949	-14.048	1.00	71.55 O
HETATM	2389	O	HOH	161	12.156	-20.278	36.293	1.00	63.41 O
HETATM	2390	O	HOH	162	12.064	0.618	21.733	1.00	59.67 O
HETATM	2391	O	HOH	163	13.025	12.470	18.298	1.00	57.94 O
HETATM	2392	O	HOH	164	11.241	-6.036	37.279	1.00	66.37 O
HETATM	2393	O	HOH	165	15.326	30.761	7.083	1.00	72.54 O
HETATM	2394	O	HOH	166	24.166	26.288	8.146	1.00	80.46 O
HETATM	2395	O	HOH	167	18.532	37.307	28.877	1.00	52.52 O
HETATM	2396	O	HOH	169	19.929	10.591	15.027	1.00	79.89 O
HETATM	2397	O	HOH	171	18.161	19.995	12.208	1.00	88.12 O
HETATM	2398	O	HOH	172	25.181	-23.987	37.247	1.00	83.59 O
HETATM	2399	O	HOH	174	18.136	-3.696	37.260	1.00	58.69 O
HETATM	2400	O	HOH	175	9.790	35.898	8.924	1.00	68.04 O
HETATM	2401	O	HOH	176	39.649	55.783	-13.588	1.00	75.74 O
HETATM	2402	O	HOH	177	11.431	-13.326	32.112	1.00	68.92 O
HETATM	2403	O	HOH	178	15.462	13.080	15.436	1.00	72.04 O
HETATM	2404	O	HOH	179	10.845	-23.387	30.834	1.00	75.68 O
HETATM	2405	O	HOH	180	8.771	-8.704	37.430	1.00	69.36 O
HETATM	2406	O	HOH	181	21.236	41.306	-18.704	1.00	71.93 O
HETATM	2407	O	HOH	182	15.632	39.325	24.779	1.00	76.42 O
HETATM	2408	O	HOH	184	9.633	7.268	24.170	1.00	59.85 O
HETATM	2409	O	HOH	185	8.212	-4.659	26.095	1.00	73.13 O
HETATM	2410	O	HOH	187	22.544	-23.667	22.886	1.00	67.43 O
HETATM	2411	O	HOH	190	38.135	52.923	-18.866	1.00	60.86 O
HETATM	2412	O	HOH	192	13.987	-13.566	39.379	1.00	64.17 O
HETATM	2413	O	HOH	194	8.678	19.753	34.818	1.00	74.26 O
HETATM	2414	O	HOH	195	16.248	11.313	17.210	1.00	71.99 O
HETATM	2415	O	HOH	196	21.583	37.449	-18.466	1.00	74.25 O
HETATM	2416	O	HOH	197	18.608	13.183	13.886	1.00	69.55 O
HETATM	2417	O	HOH	199	32.100	47.030	-11.918	1.00	55.13 O
HETATM	2418	O	HOH	200	8.309	-2.904	23.865	1.00	78.50 O
HETATM	2419	O	HOH	201	27.690	42.102	3.955	1.00	77.78 O
HETATM	2420	O	HOH	204	13.069	56.872	-6.846	1.00	79.77 O
HETATM	2421	O	HOH	205	13.299	3.871	18.787	1.00	66.67 O
HETATM	2422	O	HOH	206	29.245	60.023	-30.224	1.00	60.72 O
HETATM	2423	O	HOH	208	14.879	-4.423	17.190	1.00	90.36 O
HETATM	2424	O	HOH	209	10.483	17.298	32.627	1.00	73.09 O
HETATM	2425	O	HOH	210	11.855	61.308	-30.434	1.00	88.84 O
HETATM	2426	O	HOH	211	13.217	40.439	25.017	1.00	85.86 O
HETATM	2427	O	HOH	213	7.822	-16.528	22.942	1.00	78.51 O
HETATM	2428	O	HOH	214	23.675	20.955	33.560	1.00	73.68 O

Table 2

HETATM	2429	O	HOH	215	8.958	-13.070	31.871	1.00	66.49	O
HETATM	2430	O	HOH	216	13.965	9.052	16.630	1.00	67.53	O
HETATM	2431	O	HOH	220	8.596	-0.069	28.112	1.00	61.80	O
HETATM	2432	O	HOH	221	31.299	38.557	-18.341	1.00	61.93	O
HETATM	2433	O	HOH	222	20.516	15.336	17.249	1.00	62.41	O
HETATM	2434	O	HOH	223	32.487	45.347	-13.991	1.00	67.08	O
HETATM	2435	O	HOH	224	9.634	26.343	28.605	1.00	80.33	O
HETATM	2436	O	HOH	225	26.881	41.843	6.770	1.00	66.49	O
HETATM	2437	O	HOH	226	21.933	62.656	-9.449	1.00	77.20	O
HETATM	2438	O	HOH	227	16.939	-0.959	38.266	1.00	47.64	O
HETATM	2439	O	HOH	228	1.517	27.871	29.550	1.00	69.94	O
HETATM	2440	O	HOH	229	25.455	67.088	-17.467	1.00	70.28	O
HETATM	2441	O	HOH	231	22.761	36.354	-14.024	1.00	67.12	O
HETATM	2442	O	HOH	233	9.742	-18.263	29.864	1.00	71.11	O
HETATM	2443	O	HOH	236	9.749	-1.644	39.210	1.00	68.73	O
HETATM	2444	O	HOH	238	18.795	37.370	-0.374	1.00	70.06	O
HETATM	2445	O	HOH	239	28.893	-23.822	27.314	1.00	63.21	O
HETATM	2446	O	HOH	240	20.653	54.689	-2.794	1.00	69.17	O
HETATM	2447	O	HOH	241	32.703	57.255	-7.932	1.00	73.68	O
HETATM	2448	O	HOH	242	26.839	45.754	-28.862	1.00	73.66	O
HETATM	2449	O	HOH	243	21.145	36.229	-1.718	1.00	67.47	O
HETATM	2450	O	HOH	244	24.749	63.978	-31.459	1.00	70.06	O
HETATM	2451	O	HOH	245	15.031	42.223	-0.424	1.00	65.72	O
HETATM	2452	O	HOH	246	13.421	46.493	5.518	1.00	68.84	O
HETATM	2453	O	HOH	247	31.086	37.829	-20.633	1.00	67.16	O
HETATM	2454	O	HOH	249	16.331	24.733	8.656	1.00	80.75	O
HETATM	2455	O	HOH	250	34.686	48.482	-11.577	1.00	67.41	O
HETATM	2456	O	HOH	252	26.863	-21.667	27.711	1.00	73.87	O
HETATM	2457	O	HOH	253	25.486	24.675	5.799	1.00	94.36	O
HETATM	2458	O	HOH	255	19.570	-18.069	15.539	1.00	68.87	O
HETATM	2459	O	HOH	256	7.507	24.181	27.128	1.00	75.95	O
HETATM	2460	O	HOH	257	18.214	50.275	13.595	1.00	77.43	O
HETATM	2461	O	HOH	258	24.259	5.598	21.754	1.00	80.04	O
HETATM	2462	O	HOH	259	23.644	-9.401	38.458	1.00	73.87	O
HETATM	2463	O	HOH	260	29.288	57.908	-36.191	1.00	83.70	O
HETATM	2464	O	HOH	261	14.644	-13.020	15.667	1.00	67.62	O
HETATM	2465	O	HOH	262	16.016	47.827	16.745	1.00	77.21	O
HETATM	2466	O	HOH	263	19.538	-33.347	29.648	1.00	64.40	O
HETATM	2467	O	HOH	265	2.949	33.426	13.572	1.00	75.54	O
HETATM	2468	O	HOH	266	25.030	51.698	-23.955	1.00	72.53	O
HETATM	2469	O	HOH	267	29.126	34.667	-5.967	1.00	87.07	O
HETATM	2470	O	HOH	268	21.351	0.866	18.679	1.00	81.24	O
HETATM	2471	O	HOH	270	11.563	-28.282	33.256	1.00	88.99	O
HETATM	2472	O	HOH	273	25.953	36.560	-14.131	1.00	68.45	O
HETATM	2473	O	HOH	275	3.498	32.668	11.344	1.00	60.17	O
HETATM	2474	O	HOH	277	24.261	-20.185	20.738	1.00	69.47	O
HETATM	2475	O	HOH	279	16.935	12.111	32.241	1.00	61.50	O
HETATM	2476	O	HOH	281	6.985	31.018	33.495	1.00	82.04	O
HETATM	2477	O	HOH	282	29.259	66.155	-18.386	1.00	76.82	O
HETATM	2478	O	HOH	283	7.960	15.959	16.209	1.00	82.31	O
HETATM	2479	O	HOH	284	10.497	-27.436	17.219	1.00	87.04	O
HETATM	2480	O	HOH	286	26.964	63.396	-39.492	1.00	92.90	O
HETATM	2481	O	HOH	288	24.134	68.136	-30.170	1.00	73.68	O
HETATM	2482	O	HOH	289	21.035	57.596	-2.427	1.00	63.71	O
HETATM	2483	O	HOH	290	5.098	-6.663	9.498	1.00	71.30	O
HETATM	2484	O	HOH	291	28.355	60.022	-32.628	1.00	84.14	O
HETATM	2485	O	HOH	292	27.829	-18.993	32.106	1.00	83.61	O
HETATM	2486	O	HOH	294	25.765	53.781	-27.581	1.00	80.50	O
HETATM	2487	O	HOH	295	24.969	-15.013	17.181	1.00	79.45	O

Table 2


```
HETATM 2488  O   HOH   296      21.804 -31.840  29.638  1.00 63.37 O
HETATM 2489  O   HOH   297      24.675  41.475  22.470  1.00 76.81 O
HETATM 2490  O   HOH   298      21.097 -16.469  16.858  1.00 76.40 O
HETATM 2491  O   HOH   299      10.492   1.947  39.785  1.00 73.55 O
HETATM 2492  O   HOH   300      24.883  60.577  -6.394  1.00 83.17 O
HETATM 2493  O   HOH   301      12.022  63.003 -25.379  1.00 82.86 O
HETATM 2494  O   HOH   302      29.658  36.500 -13.658  1.00 76.81 O
HETATM 2495  O   HOH   303      28.183  35.860 -10.762  1.00 71.74 O
HETATM 2496  O   HOH   304      33.215  39.854  -9.262  1.00 79.17 O
HETATM 2497  O   HOH   305      22.138  35.777 -10.127  1.00 75.26 O
HETATM 2498  O   HOH   306      34.862  51.476  -6.285  1.00 73.10 O
HETATM 2499  O   HOH   307      40.147  51.580  -7.567  1.00 79.78 O
HETATM 2500  O   HOH   308      28.423  71.917 -29.800  1.00 75.06 O
HETATM 2501  O   HOH   309      31.298  68.573 -22.781  1.00 78.92 O
HETATM 2502  O   HOH   310      22.252  33.788   4.586  1.00 75.58 O
HETATM 2503  O   HOH   311      26.312  13.773  26.214  1.00 71.75 O
HETATM 2504  O   HOH   312      24.723  12.029  25.114  1.00 75.67 O
HETATM 2505  O   HOH   313      23.485  49.266   5.646  1.00 72.55 O
HETATM 2506  O   HOH   314      25.648  43.055  12.920  1.00 71.36 O
HETATM 2507  O   HOH   315       4.653  34.503  32.710  1.00 77.71 O
HETATM 2508  O   HOH   316       2.456  37.131  32.175  1.00 78.77 O
HETATM 2509  O   HOH   317       6.881  27.100  34.488  1.00 80.24 O
HETATM 2510  O   HOH   318      10.082  23.711  13.099  1.00 81.07 O
HETATM 2511  O   HOH   319      18.524 -28.499  21.428  1.00 79.53 O
HETATM 2512  O   HOH   321      26.684   3.017  30.716  1.00 82.34 O
HETATM 2513  O   HOH   322      27.178  -5.228  32.903  1.00 82.07 O
CONECT  174  603
CONECT  603  174
CONECT  932 1341
CONECT 1341  932
CONECT 1686 2094
CONECT 2094 1686
MASTER      303    0    0    3   27    0    0    6 2512    1    6 23
END
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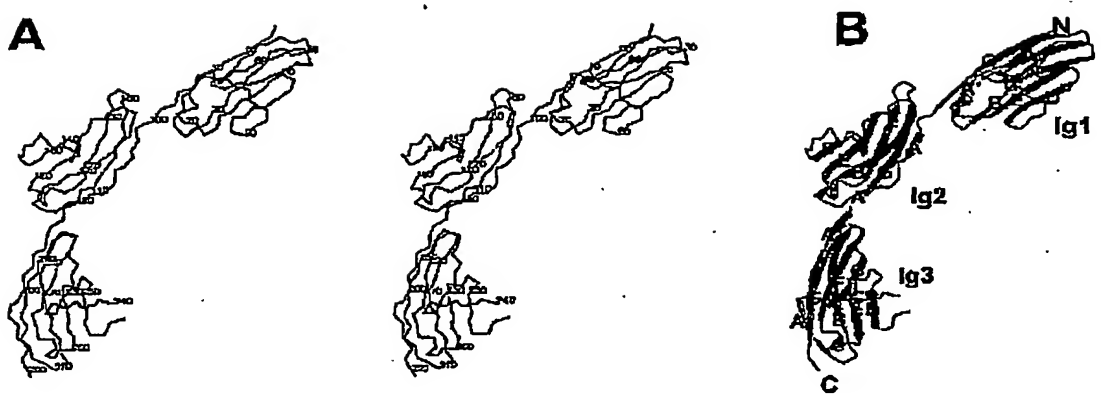


Figure 1

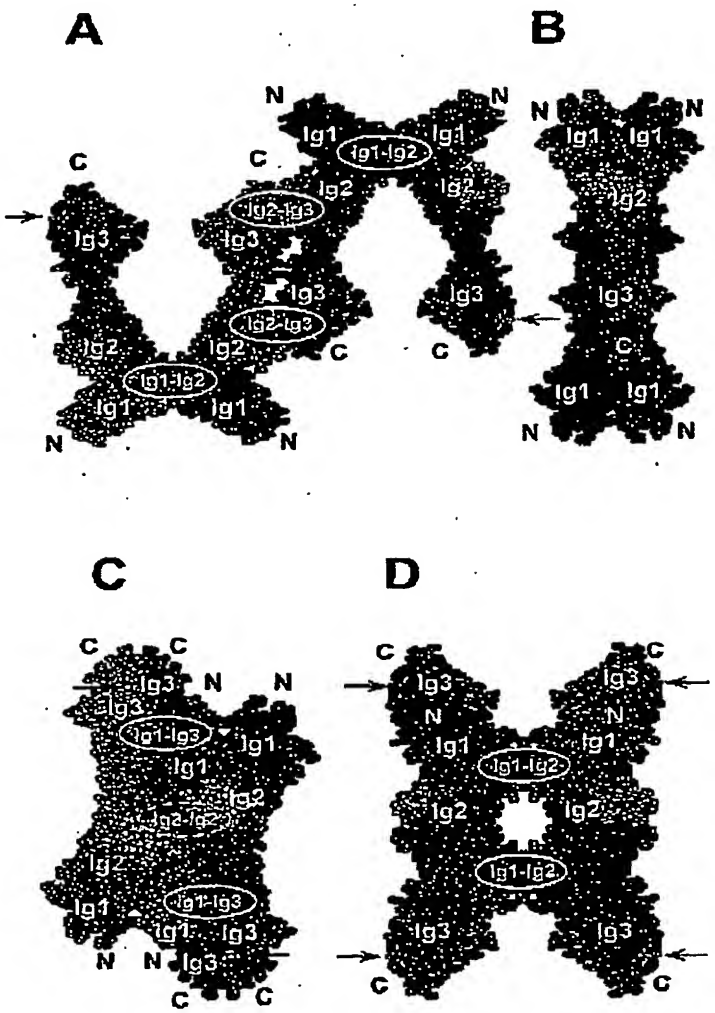


Figure 2

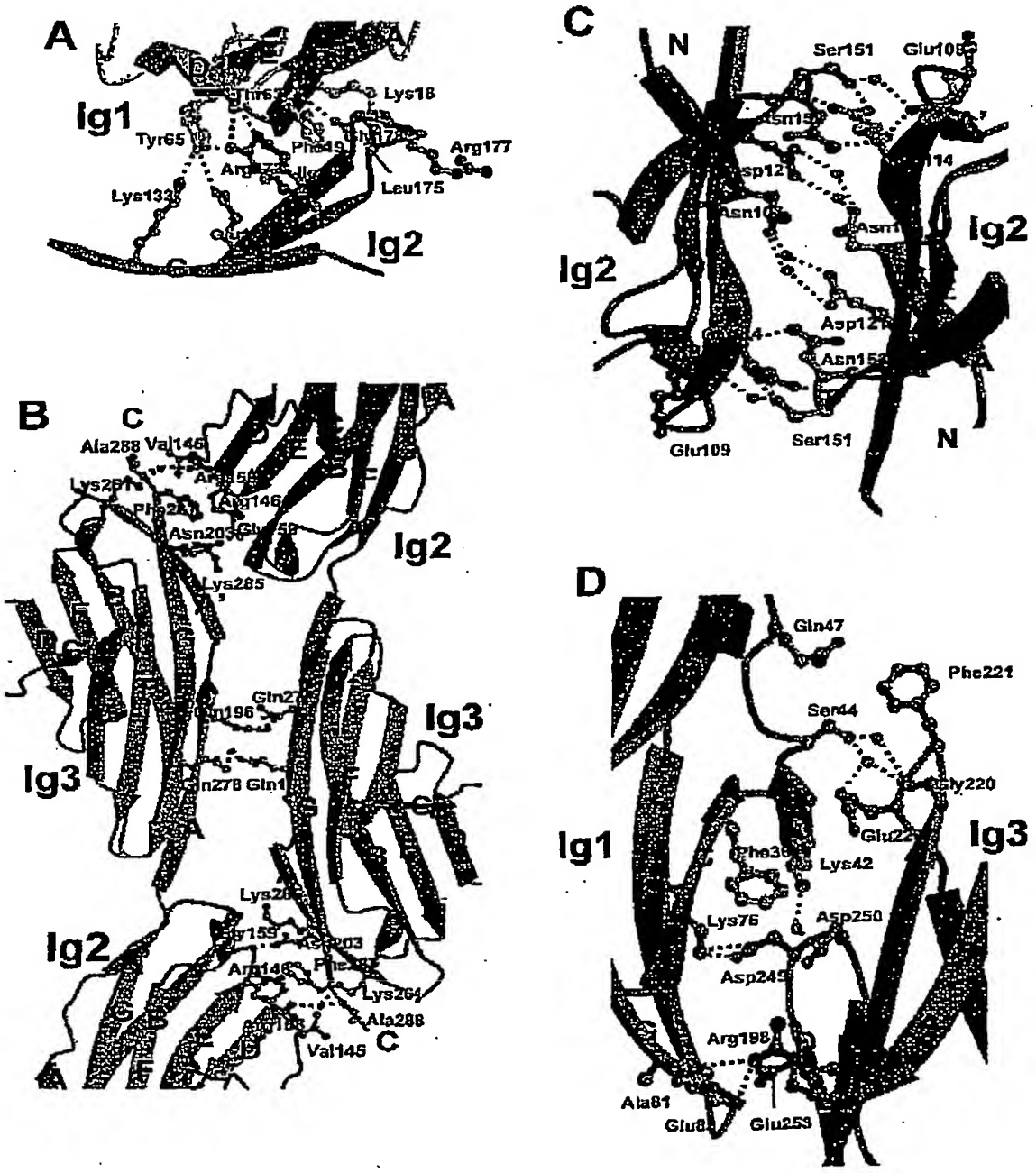
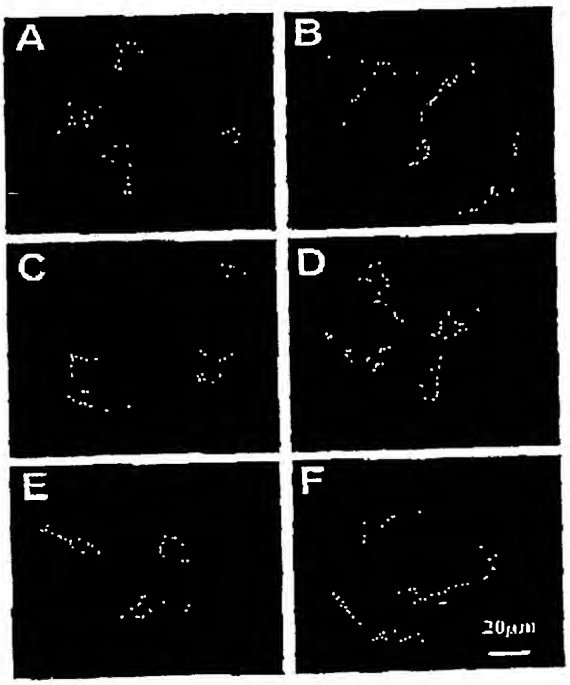


Figure 3



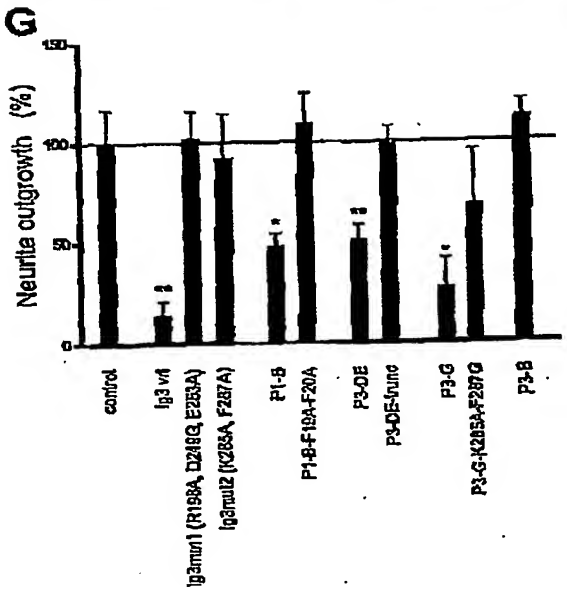


Figure 4

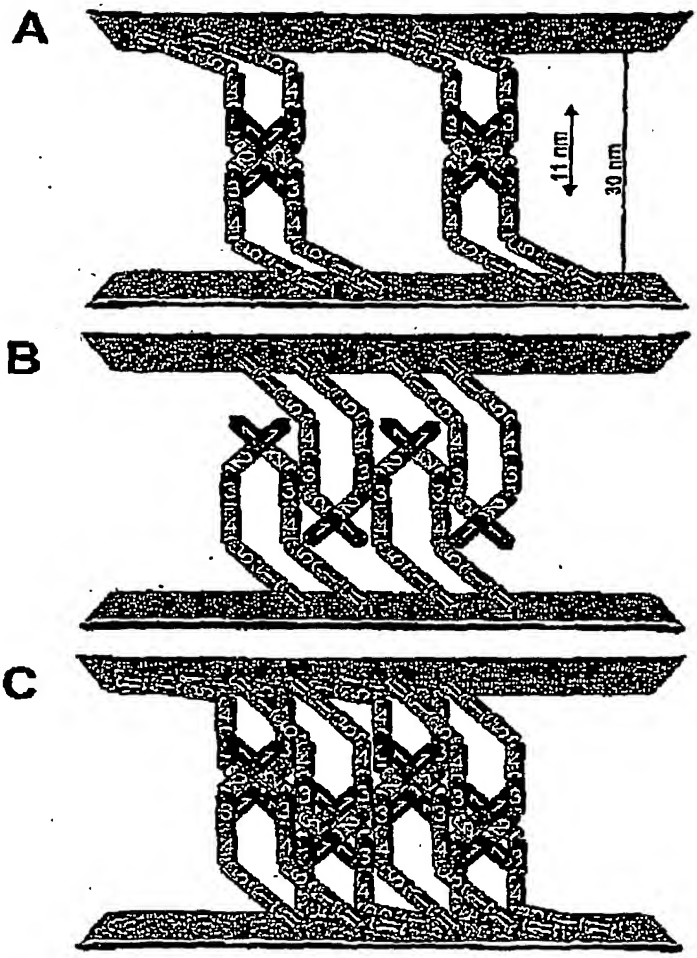


Figure 5